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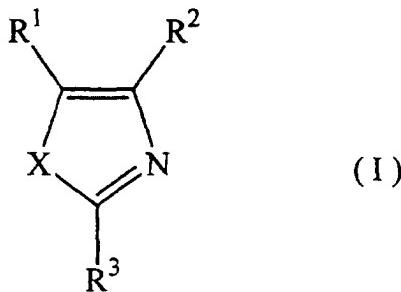
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(54) Title: LARGE CONDUCTANCE CALCIUM-ACTIVATED K CHANNEL OPENER

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(57) Abstract: A large conductance calcium-activated K channel opener comprising as an active ingredient a nitrogen-containing 5-membered heterocyclic compound represented by the following formula (I): wherein X represents N-R<sup>4</sup>, O or S, R<sup>1</sup> and R<sup>2</sup> each independently represent hydrogen, halogen, carboxyl, amino, lower alkyl, lower alkoxy carbonyl, lower alkenyl, cyclo-lower alkyl, carbamoyl, aryl, heterocyclic or heterocyclic-substituted carbonyl group, R<sup>3</sup> represents aryl, heterocyclic or lower alkyl group, and R<sup>4</sup> represents hydrogen or lower alkyl group.

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DESCRIPTION

LARGE CONDUCTANCE CALCIUM-ACTIVATED K CHANNEL OPENER

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FIELD OF THE INVENTION

This invention relates to an excellent large conductance calcium-activated K channel opener containing a nitrogen-  
10 containing 5-membered heterocyclic compound as an active ingredient, which is useful for treatment of disorders or diseases such as pollakiuria, urinary incontinence, cerebral infarction, subarachnoid hemorrhage, and the like.

15 BACKGROUND OF THE INVENTION

Potassium is the most abundant intracellular cation, and is very important in maintaining physiological homeostasis. Potassium channels are present in almost all vertebrate cells,  
20 and the potassium influx through these channels is indispensable for maintaining hyperpolarized resting membrane potential.

Large conductance calcium activated potassium channels (also  
25 BK channels or maxi-K channels) are expressed especially in neurons and smooth muscle cells. Because both of the increase of intracellular calcium concentration and membrane depolarization can activate maxi-K channels, maxi-K channels have been thought to play a pivotal role in regulating  
30 voltage-dependent calcium influx. Increase in the intracellular calcium concentration mediates many processes such as release of neurotransmitters, contraction of smooth muscles, cell growth and death, and the like. Actually, the opening of maxi-K channels causes strong membrane hyperpolarization, and  
35 inhibits these calcium-induced responses thereby. Accordingly, by inhibiting various depolarization-mediated

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physiological responses, a substance having an activity of opening maxi-K channels is expected to have potential for the treatment of diseases such as cerebral infarction, subarachnoid hemorrhage, pollakiuria, urinary incontinence, and the like.

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There have been various reports on a large conductance calcium-activated potassium channel opener, and examples of such channel opener are as follows; a pyrrole derivative disclosed in International Publication WO96/40634, a furan derivative disclosed in Japanese Provisional Patent Publication No. 2000-351773, and a nitrogen-containing 5-membered derivative in which the nitrogen atom is substituted by phenyl group or benzyl group disclosed in International Publication WO98/04135.

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Also, a compound having a similar structure to the nitrogen-containing 5-membered heterocyclic compound which is an active ingredient of the present invention has been disclosed. For example, oxazole derivatives have been reported in Japanese Provisional Patent Publications No. 36614/1984, No. 152382/1984 and No. 172488/1984, but their uses are limited only to antihypolipidemic agent. Also, in Japanese Provisional Patent Publications No. 150591/1983, No. 34951/1985 and No. 54369/1988, imidazole derivatives have been reported but their uses are limited only to a cardiotonic, an antithrombosis, an antipyretic analgesic or an anti-inflammation agent.

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#### SUMMARY OF THE INVENTION

30 An object of the present invention is to provide an excellent large conductance calcium-activated K channel opener containing a nitrogen-containing 5-membered heterocyclic compound as an active ingredient.

35 The present inventors have studied intensively to solve the problems, and as a result, they have found that a certain kind

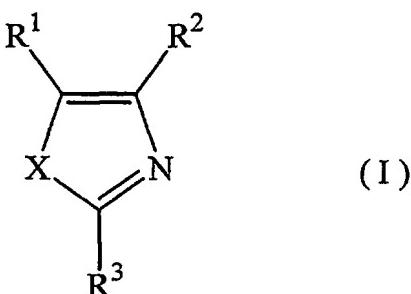
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of a nitrogen-containing 5-membered heterocyclic compound has an excellent large conductance calcium-activated K channel opening activity, whereby they have accomplished the present invention.

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That is, the present invention relates to a large conductance calcium-activated K channel opener comprising a nitrogen-containing 5-membered heterocyclic compound represented by the following formula (I):

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wherein  $X$  represents  $N-R^4$ , O or S,  $R^1$  and  $R^2$  are different from each other and each independently represents hydrogen atom, a halogen atom, carboxyl group, a substituted or unsubstituted amino group, a substituted or unsubstituted lower alkyl group, a lower alkoxy carbonyl group, a substituted or unsubstituted lower alkenyl group, a cyclo-lower alkyl group, a substituted or unsubstituted carbamoyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted heterocyclic group-substituted carbonyl group,  $R^3$  represents a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted lower alkyl group, and  $R^4$  represents hydrogen atom or a substituted or unsubstituted lower alkyl group, or a pharmaceutically acceptable salt thereof as an active ingredient.

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BEST MODE FOR CARRYING OUT THE INVENTION

In the nitrogen-containing 5-membered heterocyclic compound (I) which is an active ingredient of the present invention, the 5 aryl group is a monocyclic, dicyclic or tricyclic 6- to 14-membered aromatic hydrocarbon cyclic group, and specific examples of the aryl group may include a phenyl group, a naphthyl group and the like. Of these, a phenyl group or a naphthyl group is preferred.

10

The heterocyclic group or the heterocyclic group portion of the heterocyclic group-substituted carbonyl group is a monocyclic, dicyclic or tricyclic 6- to 14-membered aromatic hydrocarbon cyclic group, containing 1 to 4 heteroatoms selected from 15 nitrogen atom, oxygen atom and sulfur atom, which may be partially or wholly saturated.

As the monocyclic heterocyclic group, a 5- to 7-membered heterocyclic group, containing 1 to 4 hetero atoms selected from 20 nitrogen atom, oxygen atom and sulfur atom, which may be partially or wholly saturated is preferred, and specific examples of the monocyclic heterocyclic group may include furyl group, thienyl group, thiazolyl group, thiazolidinyl group, isoxazolyl group, pyrrolidinyl group, pyrrolyl group, pyridyl 25 group, pyrazinyl group, pyrimidinyl group, tetrazolyl group, and the like.

As the dicyclic heterocyclic group, a dicyclic heterocyclic group in which two of the above-mentioned monocyclic 30 heterocyclic groups are fused or a dicyclic heterocyclic group in which the above monocyclic heterocyclic group and a benzene ring are fused is preferred, and specific examples of the dicyclic heterocyclic group may include indolyl group, quinolyl group, tetrahydroquinolyl group, isoquinolyl group, 35 quinoxalyl group, benzofuryl group, dihydrobenzofuryl group, benzothienyl group, benzodioxanyl group, trihydrocyclo-

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pentathienyl group, benzothianyl group, benzothiazolyl group, imidazopyridyl group, indolyl group, indolinyl group, chromanyl group, thiophenopyridyl group, furanopyridyl group, and the like.

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As the tricyclic heterocyclic group, a tricyclic heterocyclic group in which the above-mentioned monocyclic heterocyclic group and the above-mentioned dicyclic heterocyclic group are fused or a tricyclic heterocyclic group in which the above-mentioned monocyclic heterocyclic group and two benzene rings are fused is preferred, and specific examples of the tricyclic heterocyclic group may include carbazolyl group, carbolinyl group and the like.

- 10 15 Of these heterocyclic groups, more specifically preferred are furyl group, thienyl group, thiazolyl group, isoxazolyl group, pyrrolidinyl group, pyrrolyl group, pyridyl group, pyrazinyl group, pyrimidinyl group, tetrazolyl group, indolyl group, quinolyl group, isoquinolyl group, benzofuryl group,
- 20 25 benzothienyl group, dihydrobenzofuryl group, thiophenopyridyl group and benzodioxanyl group.

- As a substituent for the amino group of R<sup>1</sup> or R<sup>2</sup>, there may be mentioned, for example, a group selected from formyl group, a lower alkyl group, a lower alkanoyl group, a lower alkylsulfonyl group and a lower alkoxy carbonyl group.

- 30 As a substituent for the lower alkyl group, there may be mentioned, for example, a group selected from a halogen atom, hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, aminosulfonyl group, a halogenosulfonyl group, amidinothio group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group,
- 35 trifluoromethyl group, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group,

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a lower alkylsulfonylamino group, a lower alkoxy carbamoyl group, a lower alkylsulfonylcarbamoyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxy carbonyl group, a heterocyclic group, a heterocyclic group-substituted carbamoyl group, a heterocyclic group-substituted lower alkylcarbamoyl group and a heterocyclic group-substituted sulfonylcarbamoyl group.

As a substituent for the lower alkenyl group, there may be mentioned, for example, carboxyl group or a lower alkoxy carbonyl group.

As a substituent for the carbamoyl group, there may be mentioned, for example, a group selected from a lower alkyl group, a lower alkoxy group and a lower alkylsulfonyl group.

As a substituent for the aryl group, there may be mentioned, for example, a group selected from nitro group, amino group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, trifluoromethyl group, a lower alkoxy carbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkylsulfonylamino group and a phenyl-lower alkoxy group.

As a substituent for the heterocyclic group, there may be mentioned, for example, a group selected from nitro group, amino group, hydroxyl group, formyl group, carbamoyl group, cyano group, carboxyl group, a lower alkoxy carbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl

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group and a mono- or di-lower alkylsulfamoyl group.

As a substituent on the heterocyclic group for the heterocyclic group-substituted carbonyl group, there may be mentioned, for  
5 example, a group selected from nitro group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, a lower alkoxy carbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkanoyl group, a mono- or di-lower alkylamino group, a mono-  
10 or di-lower alkanoyl amino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group.

The above-mentioned amino group, lower alkyl group, carbamoyl  
15 group, aryl group, heterocyclic group and heterocyclic group-substituted carbonyl group may be substituted by the same or different 1 to 3 above-mentioned substituents.

As a substituent for the aryl group of R<sup>3</sup>, there may be mentioned,  
20 for example, a group selected from cyano group, nitro group, amino group, a halogen atom, trifluoromethyl group, carboxyl group, hydroxyl group, carbamoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group, a lower alkanoyl group, a lower alkanoyloxy group, a lower alkanoyloxy-lower alkyl group, sulfo group, a lower alkylthio group, a lower alkylthio-lower alkyl group, a lower alkylsulfonyl group, a lower alkylsulfamoyl  
25 group and a lower alkylsulfinyl group.

As a substituent for the heterocyclic group, there may be mentioned, for example, a group selected from oxo group, cyano group, nitro group, amino group, a halogen atom, carboxyl group, hydroxyl group, formyl group, carbamoyl group, a mono- or di-lower alkylamino group, a N-lower alkyl-N-cyclo-lower

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- alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkyl group, a lower alkoxycarbonyl group,  
5 a lower alkanoyl group, sulfo group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group, a lower alkylsulfinyl group and a heterocyclic group.

- As a substituent for the alkyl group, there may be mentioned,  
10 for example, a group selected from hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a  
15 halogen atom, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxycarbonyl group and a heterocyclic group.  
20 The above-mentioned aryl group, heterocyclic group and lower alkyl group may be substituted by the same or different above-mentioned 1 to 3 substituents.

- As a substituent for the lower alkyl group of R<sup>4</sup>, there may be  
25 mentioned a mono- or di-lower alkylamino group. The lower alkyl group may be substituted by the same or different above-mentioned 1 to 2 substituents.

- Of the compounds (I) which are active ingredients of the present  
30 invention, preferred compounds may be compounds wherein X is N-R<sup>4</sup>, O or S; R<sup>1</sup> or R<sup>2</sup> is independently hydrogen atom, a lower alkyl group, a lower alkyl group substituted by a heterocyclic group, a di-lower alkylamino group, a carboxy-lower alkyl group, a halogeno-lower alkyl group, a lower alkoxy-lower alkyl group,  
35 a lower alkylsulfinyl-lower alkyl group, a lower alkyl-sulfonyl-lower alkyl group, a lower alkylthio-lower alkyl group,

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- atom and a di-lower alkoxy group, a heterocyclic group, a halogeno-heterocyclic group, a lower alkyl-heterocyclic group, a hydroxy-lower alkyl-heterocyclic group, a heterocyclic group substituted by a halogen atom and a lower alkyl group, a heterocyclic group substituted by a lower alkyl group and a hydroxy-lower alkyl group, or a heterocyclic group-substituted carbonyl group; R<sup>3</sup> is a halogenoaryl group, a hydroxyaryl group, a cyanoaryl group, a lower alkylaryl group, a lower alkoxyaryl group, a lower alkylthioaryl group, an aryl group substituted by a hydroxyl group and a lower alkoxy group, a heterocyclic group, a cyano-heterocyclic group, a halogeno-heterocyclic group, a lower alkyl-heterocyclic group, a di-lower alkyl-heterocyclic group, a hydroxy-lower alkyl-heterocyclic group, a di-lower aralkylamino-heterocyclic group, a heterocyclic group substituted by a halogen atom and a sulfo group, a heterocyclic group substituted by a halogen atom and a sulfamoyl group, or a heterocyclic group substituted by a halogen atom and a lower alkyl group; and R<sup>4</sup> is hydrogen atom or a lower alkyl group.
- 20 Of these, particularly preferred compounds are compounds wherein X is O or S; R<sup>1</sup> or R<sup>2</sup> is independently a carboxy-lower alkyl group, a lower alkyl group substituted by a heterocyclic group, an aryl group, a halogenoaryl group, a di-halogenoaryl group, a di-lower alkoxyaryl group, a lower alkylthioaryl group, a heterocyclic group, a halogeno-heterocyclic group, or a lower alkyl-heterocyclic group; and R<sup>3</sup> is a halogenoaryl group, a lower alkylaryl group, a di-lower alkylaminoaryl group, a lower alkylthioaryl group, a lower alkoxyaryl group, a heterocyclic group, a halogeno-heterocyclic group, a lower alkyl-heterocyclic group, a lower alkoxy-heterocyclic group, a lower alkylthio-heterocyclic group, or a di-lower alkylamino-heterocyclic group.
- 35 Among the nitrogen-containing 5-membered heterocyclic compounds (I), more preferred compounds in view of

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pharmaceutical effects are compounds wherein R<sup>1</sup> is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxy carbonyl group or a heterocyclic group, (2) an aryl group which may be substituted by one or two halogen atoms, or (3) a heterocyclic group which may be substituted by a halogen atom, R<sup>2</sup> is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxy carbonyl group or a heterocyclic group, (2) a heterocyclic group which may be substituted by a halogen atom, or (3) an aryl group which may be substituted by one or two halogen atoms; R<sup>3</sup> is (1) a heterocyclic group which may be substituted by one or two groups selected from amino group, a halogen atom, a lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group and a lower alkylthio group, or (2) an aryl group which may be substituted by amino group, a halogen atom, a lower alkyl group, a lower alkylthio group, a lower alkoxy group or a mono- or di-lower alkylamino group; and R<sup>4</sup> is hydrogen atom or a lower alkyl group.

Of these, more preferred compounds are compounds wherein R<sup>1</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxy-carbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a phenyl group which may be substituted by one or two halogen atoms, or (5) a thienyl group which may be substituted by a halogen atom; R<sup>2</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxy carbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a thienyl group which may be substituted by a halogen atom, or (5) a phenyl group which may be substituted by one or two halogen atoms; and R<sup>3</sup> is (1) a benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkyl group, a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group or a lower alkylthio group, (5) a thienyl group which may be

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substituted by one or two lower alkyl groups, (6) thieno[3,2-b]pyridyl group, (7) benzofuryl group, (8) dihydrobenzofuryl group or (9) an indolyl group which may be substituted by a lower alkyl group.

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Of these, particularly preferred compounds are compounds wherein X is O or S; R<sup>1</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a phenyl group which may be substituted by one or two halogen atoms, or (4) 10 a thienyl group which may be substituted by a halogen atom; R<sup>2</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxy-carbonyl-lower alkyl group, (3) a thienyl group which may be substituted by a halogen atom, or (4) a phenyl group which may be substituted by one or two halogen atoms; and R<sup>3</sup> is (1) a 15 benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkoxy group or a di-lower alkylamino group, (4) a 20 pyrimidinyl group which may be substituted by a di-lower alkylamino group, (5) a thienyl group which may be substituted by a di-lower alkyl group, (6) thieno[3,2-b]pyridyl group, or (7) an indolyl group which may be substituted by a lower alkyl group.

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The most preferred compound in view of pharmaceutical effects is the compound selected from the group consisting of:  
4-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)thiazol-5-yl acetic acid,  
30 5-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)-oxazol-4-yl acetic acid,  
4-(5-chlorothiophen-2-yl)-2-(4-methoxyphenyl)thiazol-5-yl acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-35 oxazol-4-yl acetic acid,  
4-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyrimidin-

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- 5-yl)thiazol-5-yl acetic acid,  
4-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyridin-5-yl)thiazol-5-yl acetic acid,  
5-(4-chlorophenyl)-2-(4-fluorophenyl)oxazol-4-yl acetic  
5 acid,  
5-(4-chlorophenyl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic  
acid,  
4-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)oxazol-5-yl  
acetic acid,  
10 5-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)oxazol-4-yl acetic acid,  
4-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)-  
thiazol-5-yl acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)oxazol-4-yl  
15 acetic acid,  
4-(4-chlorophenyl)-2-(4-methoxyphenyl)thiazol-5-yl acetic  
acid,  
5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-4-yl  
acetic acid,  
20 5-(5-chlorothiophen-2-yl)-2-(6-fluorobenzo[b]thiophene-2-  
yl)oxazol-4-yl acetic acid,  
5-(3-thienyl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(2-thieno[3,2-b]pyridyl)-  
oxazol-4-yl acetic acid,  
25 5-(3-fluoro-4-chlorophenyl)-2-(2-benzo[b]thienyl)oxazol-4-  
yl acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)thiazol-4-yl  
acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(4-methylthiophenyl)oxazol-4-yl  
30 acetic acid,  
4-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-5-yl  
acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(4-chlorophenyl)oxazol-4-yl  
acetic acid,  
35 4-(3-fluoro-4-chlorophenyl)-2-(4-methoxyphenyl)thiazol-5-yl  
acetic acid,

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- 4-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-thiazol-5-yl acetic acid,  
4-(3-fluoro-4-chlorophenyl)-2-(4-fluorophenyl)thiazol-5-yl acetic acid,  
5 4-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyridin-5-yl)-thiazol-5-yl acetic acid,  
4-(5-chlorothiophen-2-yl)-2-(4-N,N-dimethylaminophenyl)-thiazol-5-yl acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(N-methylindol-2-yl)oxazol-4-yl  
10 acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-thiazol-4-yl acetic acid;  
a lower alkyl ester of these compounds; and  
a pharmaceutically acceptable salt of these compounds.  
15  
In still another preferred embodiment of the present invention, X is O, one of R<sup>1</sup> and R<sup>2</sup> is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group, a lower alkoxy carbonyl-lower alkyl group or a lower alkyl group substituted by a tetrazolyl group; and R<sup>3</sup> is a substituted or unsubstituted aryl group or a substituted or unsubstituted heterocyclic group.  
20  
Of these, more preferred compounds are compounds wherein R<sup>3</sup> is (1) an aryl group which may be substituted by one or two substituents selected from a halogen atom, a di-lower alkylamino group, a lower alkylthio group and a lower alkoxy group, or (2) a heterocyclic group which may be substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group and a mono- or di-lower alkylamino group.  
25  
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Of these, particularly preferred compounds are compounds wherein one of R<sup>1</sup> and R<sup>2</sup> is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group or a lower alkoxy carbonyl-lower alkyl group; the aryl group is  
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phenyl group; and the heterocyclic group is a thienyl group, a pyridyl group, a pyrimidinyl group, a benzothienyl group, a benzofuryl group, a dihydrobenzofuryl group, an indolyl group or a thieno[3,2-b]pyridyl group.

5

Of these, further preferred compounds are compounds wherein R<sup>3</sup> is a phenyl group which is substituted by a halogen atom or a lower alkylthio group; a thienyl group which is substituted by one or two lower alkyl groups; a pyrimidinyl group which is substituted by a di-lower alkylamino group; a benzothienyl group which may be substituted by a halogen atom; an indolyl group which may be substituted by a lower alkyl group; or a thieno[3,2-b]pyridyl group.

10 15 In still another preferred embodiment of the present invention, X is S, one of R<sup>1</sup> and R<sup>2</sup> is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group, a lower alkoxy carbonyl-lower alkyl group or a lower alkyl group substituted by a tetrazolyl group, and R<sup>3</sup> is a substituted or

20 25 unsubstituted heterocyclic group, where said heterocyclic group is selected from a pyridyl group, a pyrimidinyl group, a benzothienyl group, an indolyl group and a thieno[3,2-b]-pyridyl group.

25 30 In a more preferred embodiment, R<sup>3</sup> is a heterocyclic group which may be substituted by one or two substituents selected from a halogen atom, a lower alkoxy group, a mono- or di-lower alkyl group, a lower alkylthio group and a mono- or di-lower alkylamino group, where said heterocyclic group is selected from a pyridyl group, a pyrimidinyl group, a benzothienyl group, and a thieno[3,2-b]pyridyl group.

In a further preferred embodiment, one of R<sup>1</sup> and R<sup>2</sup> is a thienyl

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group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group or a lower alkoxy carbonyl-lower alkyl group; R<sup>3</sup> is a pyridyl group which may be substituted by a di-lower alkylamino group; a pyrimidinyl group which may be substituted by a mono- or di-lower alkylamino group; or a benzothienyl group which may be substituted by a halogen atom.

- In the compound (I), an optical isomer based on an asymmetric carbon may be present depending on a kind of a substituent(s).
- 10 Either of the optical isomer or a mixture thereof may be used as the active ingredient of the present invention.

The active ingredient (I) of the present invention can be used in the free form or in the form of a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts of the compound (I) include inorganic acid salts such as hydrochloride, sulfate, phosphate or hydrobromide, and organic acid salts such as acetate, fumarate, oxalate, citrate, methanesulfonate, benzenesulfonate, tosylate or maleate. In addition, in case of a compound with substituents such as a carboxyl group, salts with a base (for example, alkali metal salts such as a sodium salt and a potassium salt or alkaline earth metal salts such as a calcium salt) can be mentioned.

20

25 The compound (I) or pharmaceutically acceptable salts thereof includes its internal salts, addition products, solvates and hydrates.

30 The active ingredient (I) of the present invention or pharmaceutically acceptable salts thereof can be administered orally or parenterally and used as common pharmaceutical preparations such as tablets, granules, capsules, powders, injection solution and inhalants.

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As a pharmaceutically acceptable carrier for a preparation of oral administration, there may be mentioned a material commonly used, for example, a binder (such as syrup, Gum Arabic, gelatin, sorbit, tragacanth and polyvinyl pyrrolidone), an excipient 5 (such as lactose, sugar, corn starch, potassium phosphate, sorbit and glycine), a lubricant (such as magnesium stearate, talc, polyethylene glycol and silica), a disintegrator (such as potato starch) and a humectant (such as lauryl sodium sulfate).

10

On the other hand, when the active ingredient of the present invention is administered non-orally, it may be formulated into the form of an injection or a drip infusion by using distilled water for injection, physiological saline, an aqueous glucose 15 solution and the like, or a suppository.

A dose of the compound (I) or a pharmaceutically acceptable salt thereof may vary depending on an administration method, an age, weight, conditions or a kind or degree of disease of a patient, 20 and generally about 0.1 to 50 mg/kg per day, more preferably about 0.3 to 30 mg/kg per day.

The compound (I) or a pharmaceutically acceptable salt thereof has an excellent large conductance calcium-activated K 25 channel opening activity and hyperpolarizes a membrane electric potential of cells, so that it may be used for a prophylactic, relief and/or treatment agent of, for example, hypertension, asthma, premature birth, irritable bowel syndrome, chronic heart failure, angina, cardiac infarction, cerebral infarction, 30 subarachnoid hemorrhage, cerebral vasospasm, cerebral hypoxia, peripheral blood vessel disorder, anxiety, male-pattern baldness, erectile dysfunction, diabetes, diabetic peripheral nerve disorder, other diabetic complication, sterility, urolithiasis and pain accompanied thereby, pollakiuria, 35 urinary incontinence, nocturnal enuresis, and the like.

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In the present specification, as the lower alkyl group, a hydroxy lower alkyl group, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkoxy sulfonyl group, a lower alkylsulfamoyl group, a lower alkylcarbamoyl group, a lower alkylamino group, or a lower alkylsulfonylamino group, there may be mentioned those which are straight or branched and having 1 to 6 carbon atoms, particularly those which are straight or branched and having 1 to 4 carbon atoms.

10

As a lower alkenyl group, a lower alkanoyl group, a lower alkanoyloxy group, a lower alkanoylamino group or a lower alkoxy carbonyl group, there may be mentioned those which are a straight or branched and having 2 to 7 carbon atoms, particularly those which are a straight or branched and having 2 to 5 carbon atoms.

As a cyclo-lower alkyl group, there may be mentioned those having 3 to 6 carbon atoms.

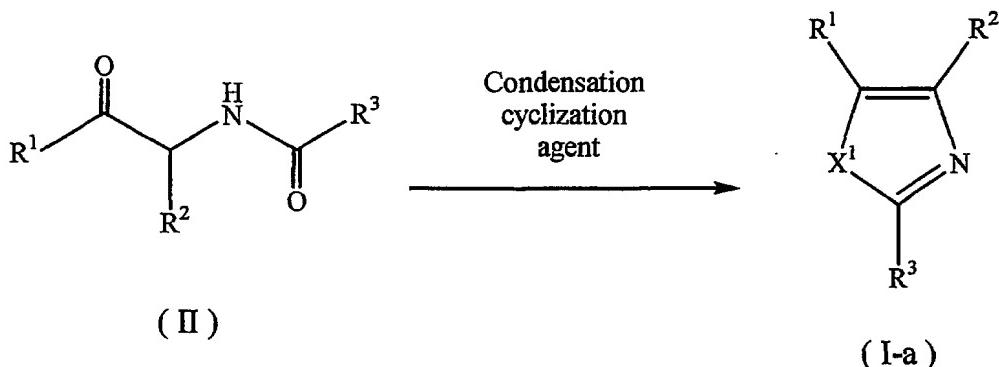
20

As a halogen atom, there may be mentioned fluorine atom, chlorine atom, bromine atom or iodine atom.

The nitrogen-containing 5-membered heterocyclic compound (I) which is an active ingredient of the present invention can be prepared by the following Method A, Method B, Method C or Method D, but the preparation methods are not limited to these methods.

30 (Method A)

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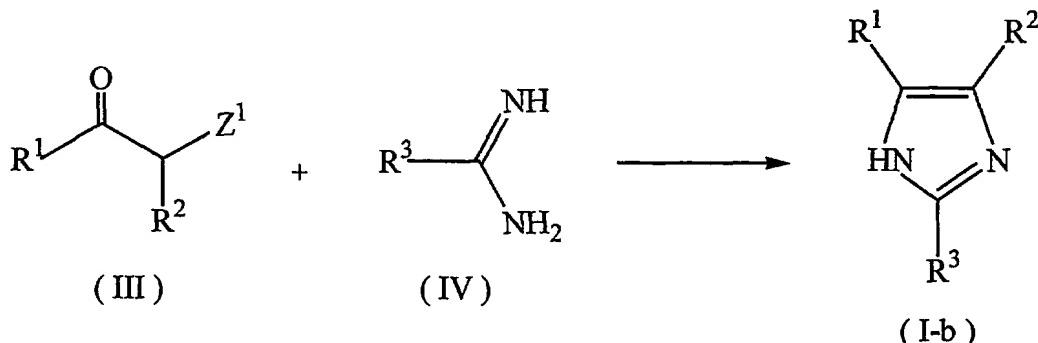
wherein X<sup>1</sup> represents NH, O or S, and other symbols have the same meanings as defined above.

- 5 Among the nitrogen-containing 5-membered heterocyclic compound (I), a compound (I-a) can be prepared by reacting the compound represented by the formula (II) or a salt thereof with a condensation reagent.
- 10 As the condensation reagent, there may be suitably used, when X<sup>1</sup> is NH, for example, ammonia or an ammonium salt (such as ammonium acetate, ammonium formate, ammonium carbonate, ammonium benzoate and ammonium picolate), when X<sup>1</sup> is O, for example, phosphorus oxychloride, thionyl chloride, acetyl
- 15 chloride, triphenylphosphine-iodine, triphenylphosphine-phosgene, sulfuric acid, polyphosphoric acid, p-toluene-sulfonic acid, etc., and when X<sup>1</sup> is S, for example, phosphorus pentasulfide, Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide), and the like.
- 20 The present reaction can be carried out in a suitable solvent or in the absence of a solvent. As the solvent, it is not particularly limited so long as it does not disturb the reaction, and there may be used, for example, acetic acid,
- 25 dimethylformamide, benzene, toluene, tetrahydrofuran, chloroform, methylene chloride, acetonitrile or a mixed solvent of the above-mentioned solvents. The present reaction proceeds suitably at 15 to 150°C, particularly at room

- 20 -

temperature to 120°C.

(Method B)



5

wherein  $\text{Z}^1$  represents a reactive residue, and other symbols have the same meanings as defined above.

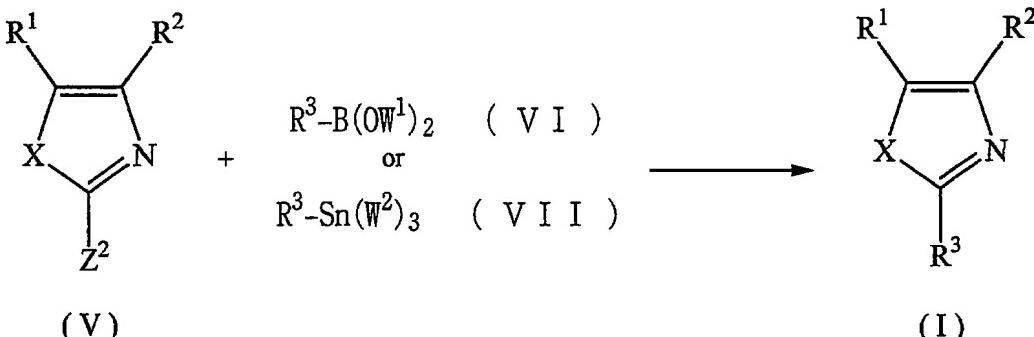
Also, among the compound (I), a compound (I-b) can be prepared  
 10 by reacting a compound represented by the formula (III) or a salt thereof with a compound represented by the formula (IV) or a salt thereof in the presence of a base. As the base, there may be suitably used, for example, an alkali metal carbonate, an alkali metal hydride, an alkali metal alkoxide, an alkali  
 15 metal hydroxide, and the like.

The present reaction can be carried out in a suitable solvent or in the absence of a solvent. As the solvent, it is not particularly limited so long as it does not disturb the reaction,  
 20 and there may be used, for example, acetonitrile, methanol, ethanol, chloroform, methylene chloride, dimethylformamide, acetone, tetrahydrofuran or a mixed solvent of the above-mentioned solvents. The present reaction proceeds suitably at 30 to 150°C, particularly at 60 to 120°C.

25

(Method C)

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(V)

(I)

wherein Z<sup>2</sup> represents a reactive residue, W<sup>1</sup> represents hydrogen atom or a lower alkyl group, W<sup>2</sup> represents a lower alkyl group, and other symbols have the same meanings as defined above.

5

The compound (I) can be also prepared by reacting a compound represented by the formula (V) with a compound represented by the formula (VI) or a compound represented by the formula (VII) 10 in the presence of a palladium catalyst. As the palladium catalyst, there may be suitably used a zero-valent or divalent palladium catalyst, for example, tetrakis(triphenylphosphine) palladium (0), bis(triphenylphosphine)palladium (II) chloride, palladium (II) acetate, etc.

15

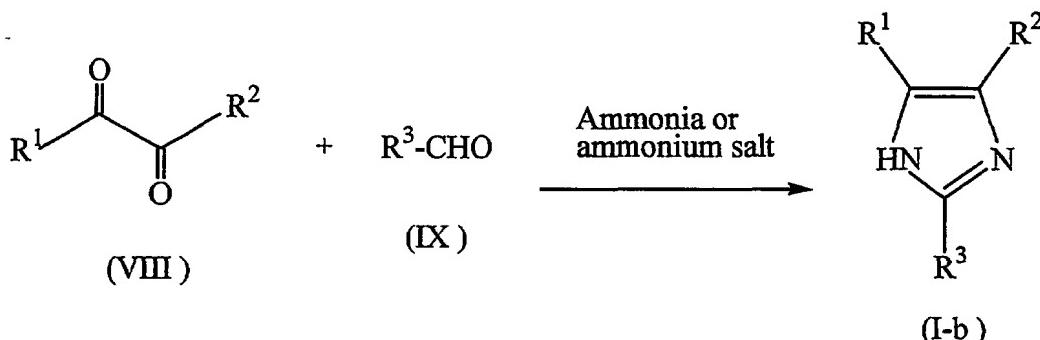
When Method C is carried out by using the compound (VI), it is preferably carried out in the presence of a base. As the base, there may be suitably used, for example, an inorganic base such as an alkali metal carbonate, an alkali metal hydroxide, an 20 alkali metal phosphate, an alkali metal fluoride, and the like, or an organic base such as triethylamine, and the like.

The present reaction can be carried out in a suitable solvent or in the absence of a solvent. As the solvent, it is not particularly limited so long as it does not disturb the reaction, and there may be used, for example, dimethoxyethane, tetrahydrofuran, dimethylformamide, methanol, ethanol, toluene, benzene, chloroform or a mixed solvent of the above-mentioned solvents. The present reaction proceeds suitably at 60 to 150°C,

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particularly at 80 to 120°C.

(Method D)



5 wherein the symbols have the same meanings as defined above.

Also, among the compound (I), a compound (I-b) can be prepared  
 10 by reacting a compound represented by the formula (VIII) or a salt thereof with a compound represented by the formula (IX) and a salt thereof in the presence of ammonia or an ammonium salt.

As the ammonium salt, there may be suitably used, for example,  
 15 ammonium acetate, ammonium formate, ammonium carbonate, ammonium benzoate, ammonium picolate, and the like.

The present reaction can be carried out in a suitable solvent or in the absence of a solvent. As the solvent, it is not  
 20 particularly limited so long as it does not disturb the reaction, and there may be used, for example, acetic acid, methanol, ethanol, dimethoxyethane, tetrahydrofuran, dimethylformamide or a mixed solvent of the above-mentioned solvents. The present reaction proceeds suitably at 0 to 150°C, particularly at 30  
 25 to 120°C.

In the above-mentioned Methods A to D, the compounds (II), (III), (IV), (V), (VIII) or (IX) may be used as a salt of an inorganic acid such as hydrochloride, sulfate, etc., or a salt of an

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inorganic base such as an alkali metal salt, an alkaline earth metal salt, etc.

As the reactive residue of Z<sup>1</sup> and Z<sup>2</sup>, a halogen atom is suitably  
5 used.

The nitrogen-containing 5-membered heterocyclic compound (I) can be prepared by converting objective compounds obtained from one of the above methods into other objective compounds. Such  
10 conversion reactions may be suitably used depending on a substituent(s) in a compound, and it can be carried out, for example, by a conventional method as mentioned in the following Methods (a) to (v).

15 Method (a) :

A compound (I) wherein R<sup>1</sup> or R<sup>2</sup> is a halogen atom can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a hydrogen atom with a halogenating agent. As the halogenating  
20 agent, there may be suitably used bromine, chlorine, iodine, [bis(trifluoroacetoxy)iodo]benzene, N-bromosuccinic imide and the like. This reaction proceeds suitably at 0°C to 30°C.

Method (b) :

25 A compound (I) wherein R<sup>1</sup> or R<sup>2</sup> is a substituted or unsubstituted aryl group, or a substituted or unsubstituted heterocyclic group can be prepared by reaction of a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a halogen atom with a (tri-lower  
30 alkyl)(a substituted or unsubstituted aryl)tin compound, or (tri-lower alkyl)(a substituted or unsubstituted heterocyclic)tin compound in the presence of a catalyst. As the catalyst, there may be suitably used a zero-valent or divalent palladium catalyst such as bis(triphenylphosphine)palladium  
35 (II) chloride, palladium (II) acetate, tetrakis(triphenylphosphine) palladium (0), etc. Also this reaction proceeds

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more suitably in the presence of a zinc salt such as zinc chloride, zinc bromide, zinc iodide, etc. This reaction proceeds suitably at 50°C to 120°C.

- 5 Also, this reaction may be carried out by using a corresponding boric acid or its ester in place of the tin compound, in the presence of a base. As the palladium catalyst and the base, those as mentioned in the above Method C are suitably used. This reaction proceeds suitably at 60°C to 120°C.

10

Method (c):

A compound (I) wherein R<sup>1</sup> or R<sup>2</sup> is a substituted or unsubstituted heterocyclic group-substituted carbonyl group can be prepared  
15 by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a substituted carbamoyl group with a substituted or unsubstituted heterocyclyl lithium. This reaction proceeds suitably at -78°C to 30°C. The substituted or unsubstituted heterocyclyl lithium can be prepared by lithiation of a corresponding  
20 halogeno-heterocyclic compound with n-butyl lithium, etc.

Method (d):

A compound (I) where X is N-R<sup>4</sup> and R<sup>4</sup> is a substituted or  
25 unsubstituted alkyl group can be prepared by reaction of a compound (I) where corresponding X is N-R<sup>4</sup> and R<sup>4</sup> is hydrogen atom with a substituted or unsubstituted lower alkyl halide (such as a lower alkyl iodide, a lower alkyl chloride and a lower alkyl bromide) or a lower alkyl sulfonate (such as a lower alkyl  
30 trifluoromethanesulfonate and a lower alkyl methanesulfonate) in the presence of a base. As the base, there may be suitably used an alkali metal hydride, an alkali metal carbonate, an alkali metal alkoxide, an alkali metal hydroxide, and the like. This reaction proceeds suitably at 30°C to 80°C.

35

Method (e):

- 25 -

A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a formylamino group or an N-lower alkyl-N-formylamino group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is an amino group or an N-lower alkylamino group with a formic acid lower alkyl ester  
5 (such as methyl ester and ethyl ester). This reaction proceeds suitably at 60°C to 100°C.

Method (f):

10 A compound (I) where R<sup>1</sup> or R<sup>2</sup> is an N-methylamino group, an N-lower alkyl-N-methylamino group or an N-ethylamino group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a formylamino group, an N-lower alkyl-N-formylamino group or an N-acetyl-amino group with a reducing agent. As the  
15 reducing agent, there may be suitably used a borane complex (such as borane-dimethylsulfide complex), lithium aluminum hydride, and the like. This reaction proceeds suitably at 0°C to 60°C.

20 Method (g):

A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a lower alkoxy carbonylamino group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is an amino group with a lower alkoxy carbonyl halide in the presence of a base. As the base, there may be suitably used pyridine, triethylamine, an alkali metal carbonate, an alkali metal lower alkoxide, an alkali metal hydride and the like. This reaction proceeds suitably at 0°C to 30°C.  
25

30

Method (h):

A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a hydroxy-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a hydrogen atom with formaldehyde or a lower alkyl  
35 aldehyde in the presence of a base. As the base, there may be suitably used an alkali metal carbonate, an alkali metal lower

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alkoxide, triethylamine, and the like. This reaction proceeds suitably at 60°C to 120°C.

Method (i)

5

A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a halogeno-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a hydroxy-lower alkyl group with a halogenating agent. As the halogenating agent, there may be suitably used thionyl 10 chloride, thionyl bromide and the like. This reaction proceeds suitably at 0°C to 50°C.

Method (j):

15 A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a lower alkoxy-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a halogeno-lower alkyl group with a lower alkanol. As the lower alkanol, there may be suitably used methanol, ethanol and the like. This reaction proceeds suitably at 30°C 20 to 80°C.

Method (k):

25 A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a lower alkylthio-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a halogeno-lower alkyl group with a lower alkyl sulfide salt. As the lower alkyl sulfide salt, there may be suitably used an alkali metal lower alkyl sulfide such as sodium methyl sulfide and the like. This reaction is preferably 30 carried out in the presence of a base. As the base, there may be suitably used triethylamine, pyridine, an alkali metal carbonate, an alkali metal alkoxide and the like. This reaction proceeds suitably at 0°C to 60°C.

35 Method (l):

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A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a lower alkylsulfinyl-lower alkyl group or a lower alkylsulfonyl-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a lower alkylthio-lower alkyl group with an oxidizing agent.

- 5 As the oxidizing agent, there may be suitably used metachloroperbenzoic acid, aqueous hydrogen peroxide solution and the like. This reaction proceeds suitably at -20°C to 30°C.

Method (m):

10

A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a carboxy-lower alkyl group or a carboxy-lower alkenyl group can be prepared by hydrolysis of a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a lower alkoxy carbonyl-lower alkyl or a cyano-lower alkyl group or a lower alkoxy carbonyl-lower alkenyl or a cyano-lower alkenyl group with a base or an acid. As the base, an alkali metal hydroxide and the like may be suitably used. As the acid, hydrochloric acid or boron tribromide and the like may be suitably used. This reaction proceeds suitably at 0°C to 80°C.

15

Method (n):

20 A compound (I) where R<sup>3</sup> is a heterocyclic group substituted by a sulfo group can be prepared by reaction of a compound (I) where corresponding R<sup>3</sup> is a heterocyclic group (which may be substituted onto the other position of the heterocyclic ring than that to which the sulfo group is to be bonded) with halogenosulfonic acid (such as chlorosulfonic acid), and then, treating with a basic aqueous solution (such as aqueous ammonia). 25 This reaction proceeds suitably at 0°C to 50°C.

30

Method (o):

35 A compound (I) where R<sup>3</sup> is a heterocyclic group substituted by sulfamoyl group can be prepared by treating a compound (I) where corresponding R<sup>3</sup> is a heterocyclic group substituted by

chlorosulfonyl group with ammonia. This reaction proceeds suitably at 0°C to 60°C.

- Method (p):

5

A compound (I) where R<sup>1</sup>, R<sup>2</sup> or R<sup>3</sup> is a heterocyclic group substituted by a hydroxy-lower alkyl group or R<sup>1</sup> or R<sup>2</sup> is a hydroxy-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup>, R<sup>2</sup> or R<sup>3</sup> is a heterocyclic group 10 substituted by a lower alkoxy carbonyl group or corresponding R<sup>1</sup> or R<sup>2</sup> is a lower alkoxy carbonyl-lower alkyl group with a reducing agent. As the reducing agent, there may be suitably used lithium aluminum hydride, lithium borohydride, a borane complex (such as borane-dimethylsulfide complex) and the like. 15 This reaction proceeds suitably at 0°C to 60°C.

Method (q):

A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a substituted or unsubstituted carbamoyl group can be prepared by reaction of a compound (I) 20 where corresponding R<sup>1</sup> or R<sup>2</sup> is a carboxyl group with a corresponding substituted or unsubstituted amine in the presence of a condensing agent. As the condensing agent, there may be suitably used 3-ethyl-1-(3-dimethylaminopropyl)- 25 carbodiimide hydrochloride, diethylcyanophosphate and the like. This reaction proceeds suitably at 0°C to 50°C.

Method (r):

30 A compound (I) where R<sup>3</sup> is a pyridyl group substituted with a mono- or di- lower alkylamino group or R<sup>3</sup> is a pyrazinyl group substituted with a mono- or di lower alkylamino group can be prepared by reacting a compound (I) where corresponding R<sup>3</sup> is a halogenopyridyl group or a halogenopyrazinyl group with a 35 corresponding mono- or di- lower alkylamine. This reaction proceeds suitably at 30°C to 120°C.

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Method (s) :

- A compound (I) where R<sup>3</sup> is a pyrimidinyl group substituted with a mono- or di- lower alkylamino group can be prepared by reacting  
5 a compound (I) where corresponding R<sup>3</sup> is a pyrimidinyl group substituted with a lower alkylthio group with a oxidizing agent, followed by reacting the resulting compound with corresponding mono- or di- lower alkylamine. Examples of the oxidizing agent may be m-chloroperbenzoic acid, hydrogen peroxide, and the like.  
10 This reaction proceeds suitably at 0°C to 30°C.

Method (t) :

- A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a substituted or unsubstituted carbamoyl-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a carboxy-lower alkyl group with a corresponding amine in the presence of a condensing agent. Examples of the condensing agent may be 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride,  
20 diethyl cyanophosphonate, and the like. This reaction proceeds suitably at 0°C to 50°C.

Method (u) :

- 25 A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a cyano-lower alkyl group can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a carbamoyl-lower alkylamino group with a dehydrating agent. Examples of the dehydrating agent may be phosphorus oxychloride, acetic anhydride, thionyl chloride and the like.  
30 This reaction proceeds suitably at 50°C to 100°C.

Method (v) :

- A compound (I) where R<sup>1</sup> or R<sup>2</sup> is a tetrazolyl-lower alkyl group  
35 can be prepared by reacting a compound (I) where corresponding R<sup>1</sup> or R<sup>2</sup> is a cyano-lower alkyl group with an azide compound.

- 30 -

Examples of the azide compound may be sodium azide, a trialkyltin azide, a trialkylsilyl azide, and the like. This reaction proceeds suitably at 80°C to 120°C.

- 5 The reactions mentioned in the above Methods (a) to (v) can be carried out in an inert solvent to the reaction or in the absence of a solvent, which is not specifically limited, and the solvent may be mentioned, for example, methylene chloride, chloroform, tetrahydrofuran, methanol, ethanol, isopropanol, 10 dimethylformamide, dimethylsulfoxide, water, ethyl acetate, dimethoxyethane, toluene, benzene, and the like, or a mixed solvent of the above solvents.

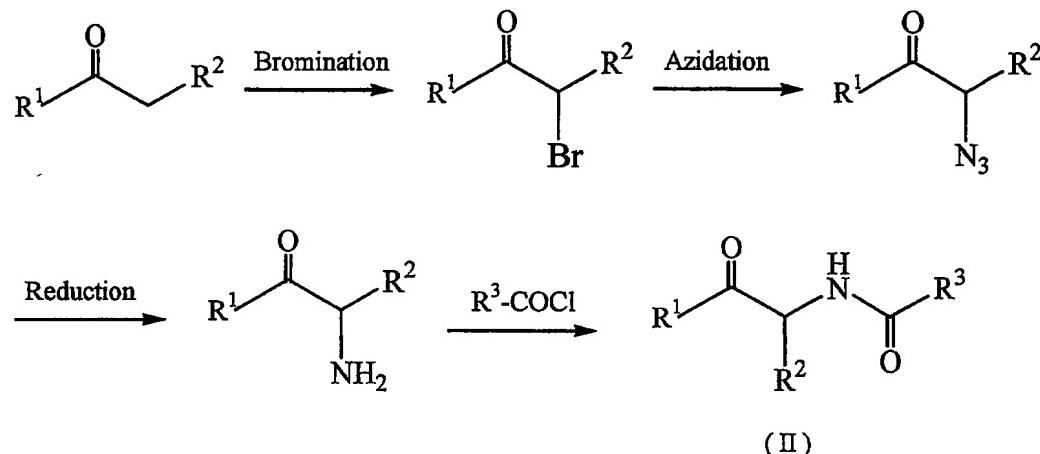
- Also, among the compounds (I), known compounds are included and 15 these known compounds have been reported in, for example, Japanese Provisional Patent Publications No. 5832/1972, No. 29771/1973, 172488/1984, 34951/1985, No. 188371/1985 and No. 167676/1986, U.S. Patents No. 3,470,195, No. 3,476,766, No. 3,546,342, No. 3,574,228 and No. 3,905,961, International 20 Publications No. WO95/04724 and No. WO99/01128, Chem.Pharm. Bull., 34(8), 3111-3120 (1986), Chem.Pharm.Bull., 36(11), 4435-4440 (1988), Chem.Pharm.Bull., 40(12), 3206-3213 (1992), Angew.Chem., 85(13), 584-585 (1973), J.Heterocyclic Chem., 22(2), 569-574 (1985), J.Med.Chem., 29(3), 333-341 (1986), 25 J.Med.Chem., 31(6), 1197-1204 (1988) and the like. However, there is no description in these references that these compounds have large conductance calcium-activated K channel opening activity.
- 30 Incidentally, the starting compound (II) or (III) of the present invention can be prepared, for example, according to the method described in J.Med.Chem., 29, 333-341 (1986), Chem.Pharm.Bull., 34(8), 3111-3120 (1986) or Japanese Provisional Patent Publication No. 167676/1986.

35

The compound (II) can be prepared specifically by the

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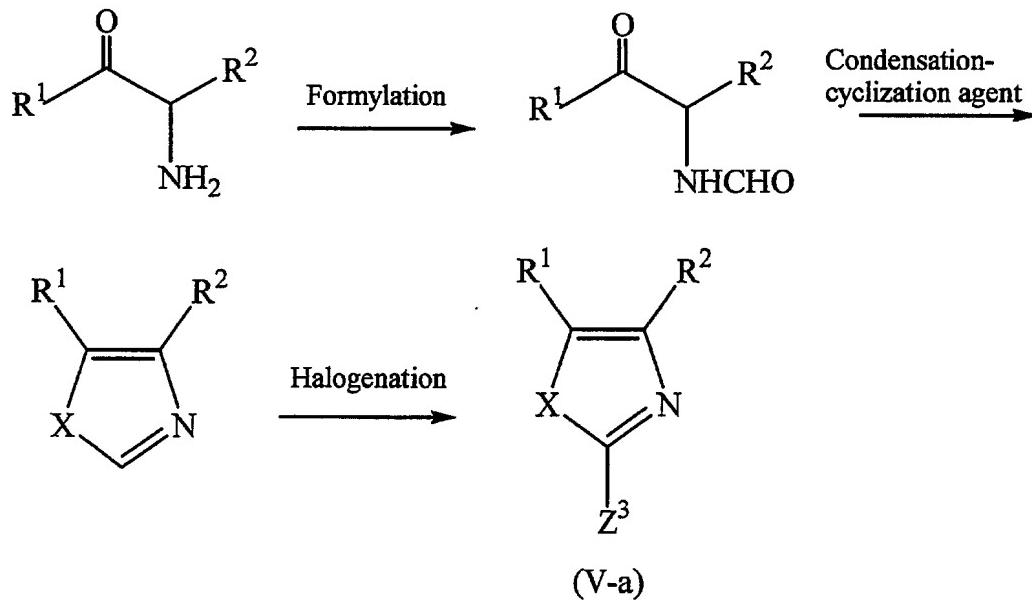
conventional method as mentioned below.



wherein the symbols have the same meanings as defined above.

5

Also, among the compounds (V), a compound (V-a) wherein  $\text{R}^2$  is a halogen atom can be prepared specifically by the conventional method as mentioned below.



10 wherein  $\text{Z}^3$  represents a halogen atom, and the other symbols have the same meaning as defined above.

The active ingredients of the present invention can be

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exemplified by the following Preparation examples but they are not limited thereto.

Preparation example

5

Preparation example 1

A crude product of 2-(6-methylnicotinoylamino)-1-(3-pyridyl)-1-butanone (425 mg) was dissolved in acetic acid (5 ml), and 10 ammonium acetate (2.30 g) was added to the solution. The resulting mixture was stirred under reflux for one hour. After cooling, 28% of aqueous ammonia was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and 15 the solvent was removed under reduced pressure. To the residue was added hydrogen chloride-methanol solution, and the solvent was again removed under reduced pressure. The resulting residue was triturated with acetone to obtain 5-ethyl-2-(2-methyl-pyridin-5-yl)-4-(3-pyridyl)imidazole trihydrochloride (369 20 mg) as pale yellowish crystalline powder.

Melting point: 270 to 273°C (decomposed)

MS·APCI (m/z): 265 (MH<sup>+</sup>)

Preparation examples 2 to 42

25

The following compounds shown in Table 1 were prepared in a manner similar to Preparation example 1 by using corresponding starting materials.

30

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Table 1

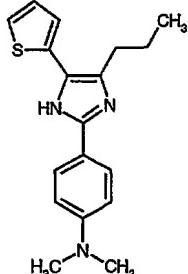
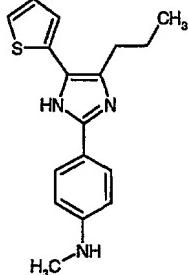
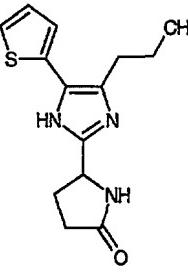
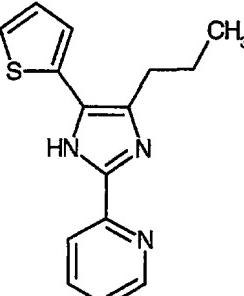
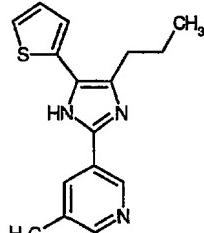
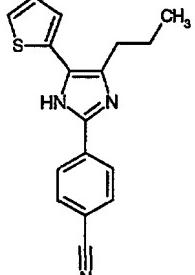
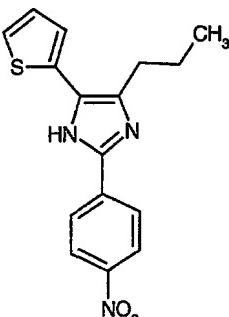
| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.  |
|-------------------------|---|------|--|
| 2                       |    | 2HCl | Crystal<br>Melting point:<br>170-172°C<br>MS·APCI (m/z) :<br>312 (M+H) + |
| 3                       |   | 2HCl | Crystal<br>Melting point:<br>175-180°C<br>MS·APCI (m/z) :<br>298 (M+H) + |
| 4                       |  | 1HCl | Crystal<br>Melting point:<br>234-237°C<br>MS·APCI (m/z) :<br>276 (M+H) + |
| 5                       |  | 1HCl | Powder<br>MS·APCI (m/z) :<br>270 (M+H) +                                 |

Table 1 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.   |
|-------------------------|---|------|---|
| 6                       |    | 2HCl | Crystal<br>Melting point:<br>275-280°C<br>MS APCI (m/z) :<br>270 (M+H) +  |
| 7                       |   | 2HCl | Crystal<br>Melting point:<br>183-185°C<br>MS ·APCI (m/z) :<br>284 (M+H) + |
| 8                       |  | 1HCl | Crystal<br>Melting point:<br>251-254°C<br>MS ·APCI (m/z) :<br>294 (M+H) + |
| 9                       |  | 1HCl | Crystal<br>Melting point:<br>278-281°C<br>MS ·APCI (m/z) :<br>314 (M+H) + |

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Table 1 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.  |
|-------------------------|--------------------|---------------|--|
| 10                      |                    | Free material | Crystal<br>Melting point:<br>127-129°C<br>MS·APCI (m/z) :<br>328 (M+H) +     |
| 11                      |                    | Free material | Crystal<br>Melting point:<br>187-189°C<br>MS·APCI (m/z) :<br>328 (M+H) +     |
| 12                      |                    | 2HCl          | Crystal<br>Melting point:<br>221-223°C<br>MS·APCI (m/z) :<br>284/286 (M+H) + |
| 13                      |                    | 2HCl          | Crystal<br>Melting point:<br>223-224°C<br>MS·APCI (m/z) :<br>284/286 (M+H) + |

Table 1 (contd.)

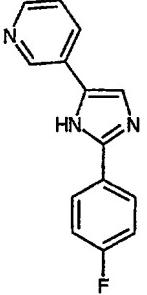
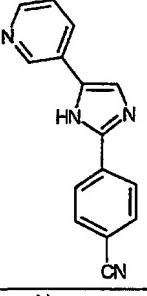
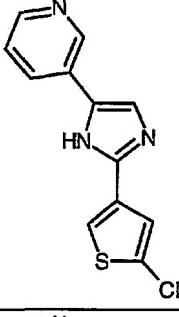
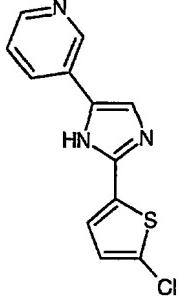
| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                  |
|-------------------------|--------------------|------|--|
| 14                      |                    | 2HCl | Powder<br>MS·APCI (m/z) :<br>290 (M+H) + |
| 15                      |                    | 2HCl | Powder<br>MS·APCI (m/z) :<br>254 (M+H) + |
| 16                      |                    | 2HCl | Powder<br>MS·APCI (m/z) :<br>281 (M+H) + |
| 17                      |                    | 2HCl | Solid<br>MS·APCI (m/z) :<br>295 (M+H) +  |

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Table 1. (contd.)

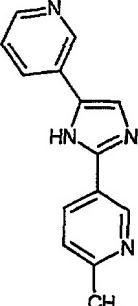
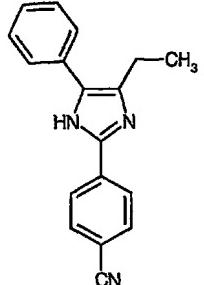
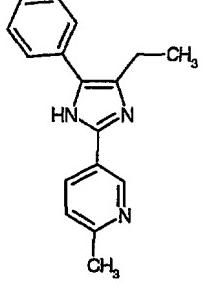
| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.  |
|-------------------------|--------------------|---------------|--|
| 18                      |                    | 2HCl          | Crystal<br>Melting point:<br>250-253°C<br>MS·APCI (m/z) :<br>293 (M+H) +     |
| 19                      |                    | 2HCl          | Crystal<br>Melting point:<br>214-216°C<br>MS·APCI (m/z) :<br>334/336 (M+H) + |
| 20                      |                    | 2HCl          | Crystal<br>Melting point:<br>215-217°C<br>MS·APCI (m/z) :<br>256 (M+H) +     |
| 21                      |                    | Free material | Powder<br>MS·APCI (m/z) :<br>308 (M+H) +                                     |

Table 1 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.   |
|-------------------------|---|------|---|
| 22                      |    | 2HCl | Crystal<br>Melting point:<br>192-195 °C<br>EI·MS (m/z) : 239 (M+)         |
| 23                      |   | 2HCl | Crystal<br>Melting point:<br>325-328 °C<br>MS·APCI (m/z) :<br>247 (M+H) + |
| 24                      |  | 2HCl | Powder<br>MS·APCI (m/z) :<br>262 (M+H) +                                  |
| 25                      |  | 2HCl | Powder<br>MS·APCI (m/z) :<br>262/264 (M+H) +                              |

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Table 1 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.  |
|-------------------------|---|------|--|
| 26                      |    | 3HCl | Crystal<br>Melting point:<br>269-273°C<br>MS·APCI (m/z) :<br>237 (M+H) + |
| 27                      |   | 1HCl | Crystal<br>Melting point:<br>285-288°C<br>MS·APCI (m/z) :<br>274 (M+H) + |
| 28                      |  | 2HCl | Crystal<br>Melting point:<br>248-251°C<br>MS·APCI (m/z) :<br>264 (M+H) + |
| 29                      |  | 1HCl | Crystal<br>Melting point:<br>202-204°C<br>MS·APCI (m/z) :<br>297 (M+H) + |

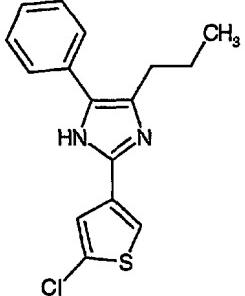
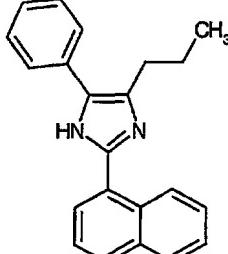
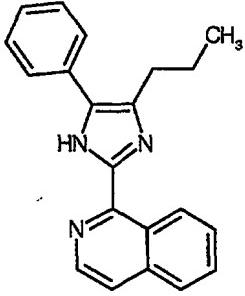
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Table 1 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.  |
|-------------------------|--------------------|------|--|
| 30                      |                    | 1HCl | Crystal<br>Melting point:<br>192-193°C<br>MS·APCI (m/z) :<br>281 (M+H) + |
| 31                      |                    | 1HCl | Crystal<br>Melting point:<br>258-260°C<br>MS·APCI (m/z) :<br>288 (M+H) + |
| 32                      |                    | 1HCl | Crystal<br>Melting point:<br>189-190°C<br>MS·APCI (m/z) :<br>313 (M+H) + |
| 33                      |                    | 1HCl | Crystal<br>Melting point:<br>215-217°C<br>MS·APCI (m/z) :<br>269 (M+H) + |

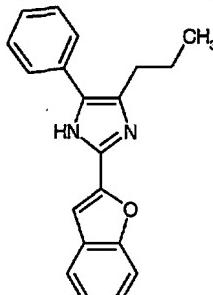
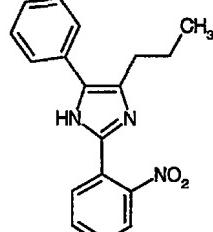
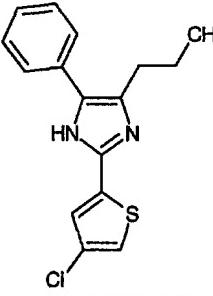
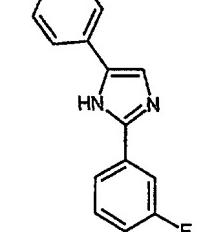
- 41 -

Table 1 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.  |
|-------------------------|---|------|--|
| 34                      |    | 1HCl | Crystal<br>Melting point:<br>194-196°C<br>MS·APCI(m/z) :<br>303/305 (M+H)+ |
| 35                      |   | 1HCl | Crystal<br>Melting point:<br>220-222°C<br>MS·APCI(m/z) :<br>252 (M+H)+     |
| 36                      |  | 1HCl | Foam<br>MS·APCI(m/z) :<br>313 (M+H)+                                       |
| 37                      |  | 1HCl | Powder<br>MS·APCI(m/z) :<br>314 (M+H)+                                     |

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Table 1 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.  |
|-------------------------|---|------|--|
| 38                      |    | 1HCl | Crystal<br>Melting point:<br>185-188°C<br>MS·APCI (m/z) :<br>303 (M+H) + |
| 39                      |   | 1HCl | Crystal<br>Melting point:<br>233-236°C<br>MS·APCI (m/z) :<br>308 (M+H) + |
| 40                      |  | 1HCl | Crystal<br>Melting point:<br>188-190°C<br>MS·APCI (m/z) :<br>303 (M+H) + |
| 41                      |  | 1HCl | Crystal<br>Melting point:<br>250-255°C<br>MS·APCI (m/z) :<br>239 (M+H) + |

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Table 1 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.  |
|-------------------------|--------------------|------|--|
| 42                      |                    | 1HCl | Crystal<br>Melting point:<br>>300°C<br>MS·APCI (m/z) : 246 (M+ H)+ |

## Preparation example 43

5                  4-Cyano-2- (4-fluorobenzoylamino)-1-(3-pyridyl)-1-butanone (500 mg) was dissolved in acetic acid (3 ml), and ammonium acetate (2.99 g) was added to the solution and the resulting mixture was refluxed overnight. After cooling, 28% of aqueous ammonia 10 was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by 15 silica gel flush column chromatography (solvent: hexane : ethyl acetate=1:2) and treated with hydrogen chloride-ethanol to obtain 5-(2-cyanoethyl)-2-(4-fluorophenyl)-4-(3-pyridyl)-imidazole dihydrochloride (172 mg) as colorless powder.  
 MS·APCI (m/z) : 293 (MH+)

## 20 Preparation examples 44 to 62

The following compounds shown in Table 2 were prepared in a manner similar to Preparation example 43 by using corresponding starting materials.

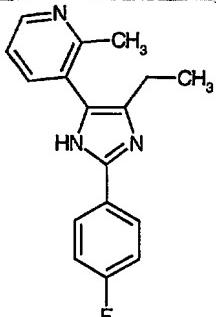
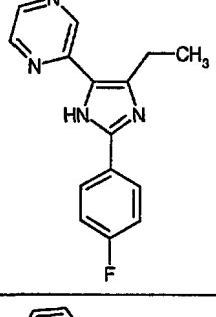
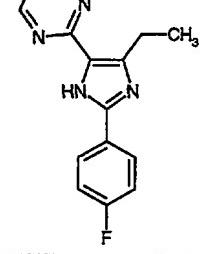
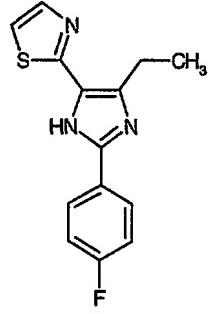
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Table 2

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.   |
|-------------------------|--------------------|---------------|---|
| 44                      |                    | Free material | Crystal<br>Melting point:<br>200-202°C<br>(Decomposed)<br>EI·MS (m/z) :<br>301 (M+) |
| 45                      |                    | Free material | Crystal<br>Melting point:<br>171-173°C<br>EI·MS (m/z) :<br>326 (M+)                 |
| 46                      |                    | 1HCl          | Powder<br>MS·APCI (m/z) :<br>298 (M+H) +  |
| 47                      |                    | 2HCl          | Crystal<br>Melting point:<br>260-262°C<br>MS·APCI (m/z) :<br>282 (M+H) +            |

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Table 2 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.  |
|-------------------------|---|------|--|
| 48                      |    | 2HCl | Powder<br>MS·APCI (m/z) :<br>282 (M+H) +                                 |
| 49                      |   | 1HCl | Crystal<br>Melting point:<br>241-243°C<br>MS·APCI (m/z) :<br>269 (M+H) + |
| 50                      |  | 1HCl | Crystal<br>Melting point:<br>190-192°C<br>MS·APCI (m/z) :<br>269 (M+H) + |
| 51                      |  | 1HCl | Crystal<br>Melting point:<br>215-218°C<br>MS·APCI (m/z) :<br>274 (M+H) + |

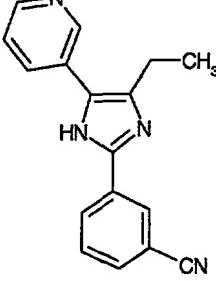
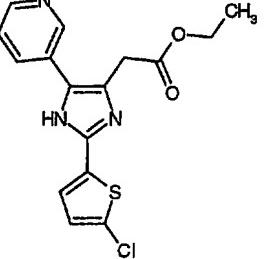
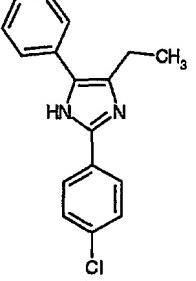
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Table 2 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.  |
|-------------------------|--------------------|------|--|
| 52                      |                    | 1HCl | Crystal<br>Melting point:<br>267-269°C<br>MS·APCI (m/z) :<br>274 (M+H) + |
| 53                      |                    | 2HCl | Powder<br>MS·APCI (m/z) :<br>275 (M+H) +                                 |
| 54                      |                    | 2HCl | Crystal<br>Melting point:<br>198-201°C                                   |
| 55                      |                    | 2HCl | Crystal<br>Melting point:<br>205-207°C<br>MS·APCI (m/z) :<br>290 (M+H) + |

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Table 2 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.   |
|-------------------------|---|---------------|---|
| 56                      |    | 2HCl          | Powder<br>MS·APCI (m/z) :<br>284 (M+H) +                                |
| 57                      |   | 2HCl          | Powder<br>MS·APCI (m/z) :<br>275 (M+H) +                                |
| 58                      |  | 2HCl          | Powder<br>MS·APCI (m/z) :<br>348 (M+H) +                                |
| 59                      |  | Free material | Crystal<br>Melting point:<br>174-176°C<br>EI·MS (m/z) :<br>282/284 (M+) |

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Table 2 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.   |
|-------------------------|--------------------|---------------|---|
| 60                      |                    | Free material | Crystal<br>Melting point:<br>147-149°C<br>EI·MS (m/z) :<br>297/299 (M+) |
| 61                      |                    | Free material | Crystal<br>Melting point:<br>169-170°C<br>EI·MS (m/z) : 266 (M+)        |
| 62                      |                    | Free material | Crystal<br>Melting point:<br>176-178°C<br>EI·MS (m/z) : 291 (M+)        |

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Preparation example 63

Under ice-cooling, phosphorus oxychloride (0.24 ml) was added  
5 dropwise to a solution of 2-(5-chlorothiophen-2-yl)amino-1-(3-pyridyl)-1-butanone (610 mg) in N,N-dimethylformamide (7 ml),  
and the resulting mixture was stirred at room temperature  
overnight and further at 60°C overnight. After cooling, the  
reaction mixture was poured into ice water, neutralized by a  
10 saturated aqueous sodium hydrogen carbonate solution and  
extracted with ethyl acetate. The organic layer was washed with  
water and brine, and then, dried over anhydrous magnesium sulfate  
and the solvent was removed under reduced pressure. The  
resulting residue was purified by silica gel column chromatogra-  
15 phy (solvent: chloroform : ethyl acetate=2:1) and treated  
with hydrogen chloride-ethanol solution to obtain 2-(5-  
chlorothiophen-2-yl)-4-ethyl-5-(3-pyridyl)oxazole hydro-  
chloride (466 mg) as pale yellowish powder.

Melting point: 201 to 204°C

20 MS·APCI (m/z): 291/293 (MH+)

Preparation examples 64 and 65

The following compounds shown in Table 3 were prepared in a manner  
25 similar to Preparation example 63 by using corresponding starting  
materials.

- 50 -

Table 3

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                  |
|-------------------------|--------------------|---------------|--|
| 64                      |                    | 1HCl          | Powder<br>MS·APCI (m/z) :<br>343 (M+H) + |
| 65                      |                    | Free material | Powder<br>MS·APCI (m/z) :<br>349 (M+H) + |

## Preparation example 66

5

- A mixture of 2-bromo-2'-methoxy-acetophenone (514 mg), 4-fluorobenzamidine hydrochloride (392 mg) and potassium carbonate (930 mg) in acetonitrile (5 ml) was refluxed for 2 hours. After cooling, to the reaction mixture were added 10 chloroform and water, the organic layer was collected and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was recrystallized from methanol to obtain 2-(4-fluorophenyl)-4-(2-methoxyphenyl)imidazole (1.54 g) as pale yellowish crystal.
- 15 This compound was treated with hydrogen chloride-ethanol solution to be converted into a hydrochloride salt form. Melting point: 165 to 167°C (free material)

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Melting point: 245 to 248°C (hydrochloride)

MS·APCI (m/z): 269 (MH+) (hydrochloride)

Preparation example 67

5

A mixture of 5-ethyl-2-iodo-4-(3-pyridyl)-imidazole (150 mg), 3-hydroxymethylthiophene-2-boric acid (105 mg) and tetrakis(triphenylphosphine)palladium (0) (58 mg) in an aqueous 2M sodium carbonate solution (1ml) and dimethoxyethane

10 (3 ml) was stirred under argon atmosphere at 100°C for 2.5 hours. After cooling, to the reaction mixture were added water and ethyl acetate. The organic layer was collected, and after washing with brine, it was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The

15 resulting residue was purified by NH silica gel flush column chromatography (solvent: ethyl acetate) and treated with hydrogen chloride-dioxane solution to obtain 5-ethyl-2-(3-hydroxymethylthiophen-2-yl)-4-(3-pyridyl)imidazole dihydrochloride (110 mg) as colorless powder.

20 MS·APCI (m/z): 286 (MH+)

Preparation examples 68

The following compounds shown in Table 4 were prepared in a  
25 manner similar to Preparation example 67 by using corresponding starting materials.

- 52 -

Table 4

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.             |
|-------------------------|--------------------|------|-------------------------------------|
| 68                      |                    | 2HCl | Powder<br>MS·APCI (m/z) : 257 (M+H) |

Preparation example 69

- 5 A mixture of ethyl 2,3-diketovalerate (8.00 g), 4-fluoro-benzaldehyde (11.30 g) and ammonium acetate (35.00 g) in acetic acid (120 ml) was stirred under argon atmosphere at 70 to 80°C for 40 minutes. After cooling, water was added to the reaction mixture and the reaction mixture was extracted with a mixed solution of ethyl acetate-diethyl ether. The organic layer was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: hexane : ethyl acetate=3:1) and recrystallized from ethyl acetate-diethyl ether to obtain ethyl 5-ethyl-2-(4-fluorophenyl)imidazol-4-carboxylate (5.16 g) as colorless crystal.
- 10 15 20 Melting point: 197 to 198°C  
MS·APCI (m/z) : 263 (MH+)

Preparation example 70

- 25 A mixture of ethyl 5-ethyl-2-(4-fluorophenyl)imidazol-4-carboxylate (2.81 g), 4N aqueous sodium hydroxide solution (14

- 53 -

ml), ethanol (35 ml) and tetrahydrofuran (15 ml) was stirred at room temperature overnight, followed by refluxing for 3 hours. 4N aqueous sodium hydroxide solution (28 ml) was added to the mixture and the mixture was refluxed overnight. After cooling, 5 the reaction mixture was concentrated under reduced pressure and neutralized by 10% hydrochloric acid, and precipitated solid was collected by filtration. The solid was dissolved in tetrahydrofuran, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting 10 residue was triturated with diethyl ether to obtain first crop of 5-ethyl-2-(4-fluorophenyl)imidazol-4-carboxylic acid (1.06 g) as colorless powder. Moreover, the filtrate was purified by HP-20 resin (trade name, available from Nippon Rensui K.K.) (solvent: water → methanol) to give second crop of 15 5-ethyl-2-(4-fluorophenyl)imidazol-4-carboxylic acid (1.60 g).

ESI·MS (m/z): 233 (M-H)

Preparation example 71

20 A mixture of 5-ethyl-2-(4-fluorophenyl)imidazol-4-carboxylic acid (600 mg), N,O-dimethylhydroxylamine hydrochloride (325 mg), 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride (540 mg), 1-hydroxybenzotriazole (381 mg) and triethylamine 25 (0.54 ml) in N,N-dimethylformamide (9 ml) was stirred at room temperature overnight. Water was added to the reaction mixture, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate, and the solvent was removed under 30 reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: hexane : ethyl acetate=2:1) to obtain 5-ethyl-2-(4-fluorophenyl)-4-(N-methoxy-N-methylcarbamoyl)imidazole (656 mg) as colorless powder.

35 MS·APCI (m/z): 278 (MH+)

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Preparation example 72

To a solution of 2-bromopyridine (855 mg) in tetrahydrofuran (16 ml) was added dropwise 1.6M n-butyl lithium (3.38 ml, hexane solution) under argon gas atmosphere at -78°C, and after stirring the mixture at the same temperature for 30 minutes, a solution of 5-ethyl-2-(4-fluorophenyl)-4-(N-methoxy-N-methylcarbamoyl)imidazole (300 mg) in tetrahydrofuran (4 ml) was added dropwise to the mixture. After the reaction mixture was stirred 10 under ice-acetone cooling for 30 minutes, a saturated aqueous ammonium chloride solution was added to the mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. 15 The resulting residue was triturated with diethyl ether-hexane to obtain 5-ethyl-2-(4-fluorophenyl)-imidazol-4-yl-(2-pyridyl)ketone (324 mg). 132 mg of the product was treated with hydrogen chloride-dioxane solution to obtain the dihydrochloride salt (73 mg) as colorless solid.

20 MS·APCI (m/z): 296 (MH+)

Preparation example 73

The following compounds shown in Table 5 were prepared in a manner 25 similar to Preparation example 72 by using corresponding starting materials.

- 55 -

Table 5

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.             |
|-------------------------|--------------------|------|-------------------------------------|
| 73                      |                    | 2HCl | Solid<br>MS·APCI (m/z) : 296 (M+H)+ |

## Preparation example 74

5

In acetonitrile (80 ml) were dissolved 2,2-dichlorobutanal (16.2 g) and 4-fluorobenzaldehyde (14.9 g). To the solution was added dropwise 28% aqueous ammonia (135 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for 4 days.

- 10 Water was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was crystallized from methanol-diethyl ether to obtain 4-ethyl-  
 15 2-(4-fluorophenyl)imidazole (9.36 g).

MS·APCI (m/z) : 191 (MH+)

## Preparation examples 75 and 76

- 20 The following compounds shown in Table 6 were prepared in a manner similar to Preparation example 74 by using corresponding starting materials.

Table 6

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.  |
|-------------------------|--------------------|---------------|--|
| 75                      |                    | 2HCl          | Solid<br>MS·APCI (m/z) : 188 (M+H) +                               |
| 76                      |                    | Free material | Crystal<br>Melting point: 168-170°C<br>MS·APCI (m/z) : 205 (M+H) + |

## Preparation example 77

5

To a suspension of 4-ethyl-2-(4-fluorophenyl)imidazole (4.90 g) in chloroform(100 ml) was added bromine (4.53 g), and the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added a saturated aqueous sodium hydrogen

- 10 carbonate solution, and the organic layer was collected . The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was crystallized from chloroform to obtain 5-bromo-4-ethyl-2-(4-fluorophenyl)-
- 15 imidazole (5.16 g) as colorless crystal. 53 mg of the product was treated with 4N hydrogen chloride-dioxane solution to obtain 5-bromo-4-ethyl-2-(4-fluorophenyl)imidazole (60 mg) as colorless crystal.

Melting point: 192 to 193°C (Free material)

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MS·APCI (m/z) : 269/271 (MH+) (Free material)

Melting point: 219 to 221°C (decomposed) (Hydrochloride)

MS·APCI (m/z) : 269/271 (MH+) (Hydrochloride)

## 5 Preparation examples 78 and 79

The following compounds shown in Table 7 were prepared in a manner similar to Preparation example 77 by using corresponding starting materials.

10

Table 7

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.   |
|-------------------------|---|------|---|
| 78                      | <p>Chemical structure of compound 78: 2-(2-methylpyridin-4-yl)-5-bromo-3-methylimidazole. It consists of a 2-methylimidazole ring system where the 2-position is substituted with a 2-methylpyridine group and the 5-position is substituted with a bromine atom.</p> | 2HCl | Solid<br>MS·APCI (m/z) : 264/266 (M+H)+                               |
| 79                      | <p>Chemical structure of compound 79: 2-(2-fluorophenyl)-5-bromo-3-methylimidazole. It consists of a 2-methylimidazole ring system where the 2-position is substituted with a 2-fluorophenyl group and the 5-position is substituted with a bromine atom.</p>         | 1HCl | Crystal<br>Melting point: 178-180°C<br>MS·APCI (m/z) : 283/285 (M+H)+ |

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Preparation example 80

A mixture of 5-bromo-4-ethyl-2-(4-fluorophenyl)imidazole (100 mg), tributyl(3-pyridyl)tin (206 mg), zinc chloride (53 mg) and 5 bis(triphenylphosphine)palladium (II) dichloride (26 mg) in N,N-dimethylformamide (3 ml) was refluxed under argon atmosphere for 5 hours. After cooling, a 10% aqueous potassium fluoride solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with 10 brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=1:4), and recrystallized from ethyl acetate-hexane and treated with hydrogen chloride-methanol solution to 15 obtain 5-ethyl-2-(4-fluorophenyl)-4-(3-pyridyl)imidazole dihydrochloride (48 mg) as colorless powder.

MS·APCI (m/z): 268 (MH<sup>+</sup>)

Preparation examples 81 to 101

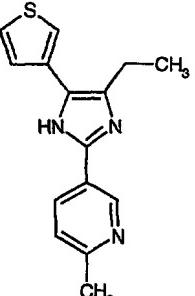
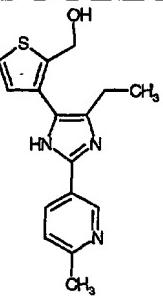
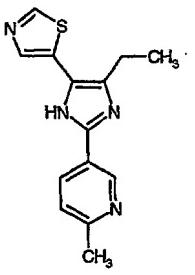
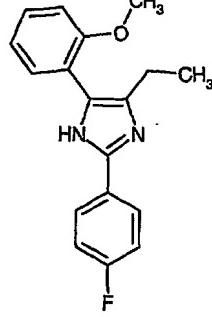
20

The following compounds shown in Table 8 were prepared in a manner similar to Preparation example 80 by using corresponding starting materials.

25

- 59 -

Table 8

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.  |
|-------------------------|---|------|--|
| 81                      |    | 2HCl | Solid<br>MS·APCI (m/z) : 270 (M+H) +   |
| 82                      |   | 2HCl | Solid<br>MS·APCI (m/z) : 300 (M+H) +   |
| 83                      |  | 2HCl | Crystal<br>Melting point: 247-251°C<br>MS·APCI (m/z) : 271 (M+H) +                 |
| 84                      |  | 1HCl | Crystal<br>Melting point: 200-203°C<br>(Decomposed)<br>MS·APCI (m/z) : 297 (M+H) + |

- 60 -

Table 8 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.  |
|-------------------------|--------------------|------|--|
| 85                      |                    | 1HCl | Crystal<br>Melting point:<br>287-289°C<br>MS·APCI (m/z) :<br>269 (M+H) + |
| 86                      |                    | 1HCl | Crystal<br>Melting point:<br>254-256°C<br>MS·APCI (m/z) :<br>274 (M+H) + |
| 87                      |                    | 1HCl | Crystal<br>Melting point:<br>233-235°C<br>MS·APCI (m/z) :<br>299 (M+H) + |
| 88                      |                    | 1HCl | Crystal<br>Melting point:<br>224-226°C<br>MS·APCI (m/z) :<br>281 (M+H) + |

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Table 8 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.  |
|-------------------------|--------------------|------|--|
| 89                      |                    | 1HCl | Crystal<br>Melting point:<br>174-176°C<br>MS·APCI (m/z) :<br>327 (M+H) + |
| 90                      |                    | 2HCl | Powder<br>MS·APCI (m/z) :<br>324 (M+H) +                                 |
| 91                      |                    | 1HCl | Crystal<br>Melting point:<br>220-222°C<br>MS·APCI (m/z) :<br>326 (M+H) + |
| 92                      |                    | 1HCl | Crystal<br>Melting point:<br>262-264°C<br>MS·APCI (m/z) :<br>331 (M+H) + |

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Table 8 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.  |
|-------------------------|--------------------|---------------|--|
| 93                      |                    | 2HCl          | Powder<br>MS·APCI (m/z) : 282 (M+H) +                              |
| 94                      |                    | 2HCl          | Powder<br>MS·APCI (m/z) : 282 (M+H) +                              |
| 95                      |                    | Free material | Crystal<br>Melting point: 240-242°C<br>MS·APCI (m/z) : 306 (M+H) + |
| 96                      |                    | 1HCl          | Crystal<br>Melting point: 120-122°C<br>MS·APCI (m/z) : 311 (M+H) + |

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Table 8 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.  |
|-------------------------|--------------------|------|--|
| 97                      |                    | 2HCl | Powder<br>MS·APCI (m/z) : 282 (M+H) +                                  |
| 98                      |                    | 2HCl | Powder<br>MS·APCI (m/z) : 339 (M+H) +                                  |
| 99                      |                    | 1HCl | Crystal<br>Melting point:<br>228-230 °C<br>MS·APCI (m/z) : 299 (M+H) + |
| 100                     |                    | 2HCl | Powder<br>MS·APCI (m/z) : 340 (M+H) +                                  |

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Table 8 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.   |
|-------------------------|--------------------|------|---|
| 101                     |                    | 1HCl | Crystal<br>Melting point:<br>186-189°C<br>MS·APCI (m/z) :<br>324 (M+H)+ |

## 5 Preparation example 102

To a solution of 5-ethyl-2-(4-fluorophenyl)-4-(3-pyridyl)-imidazole (481 mg) in N,N-dimethylformamide (7 ml) was added sodiumhydride (79 mg, 60% mineral oil) under ice-acetone cooling,  
 10 and the mixture was stirred for 15 minutes. To the mixture was added methyl iodide (307 mg) and the mixture was stirred at room temperature for one hour. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed  
 15 with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: chloroform : methanol=95:5), and treated with hydrogen chloride-methanol solution to obtain 5-ethyl-2-(4-fluoro-  
 20 phenyl)-1-methyl-4-(3-pyridyl)imidazole dihydrochloride (285 mg).

MS·APCI (m/z) : 282 (MH+)

## Preparation examples 103 and 104

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The following compounds shown in Table 9 were prepared in a manner similar to Preparation example 102 by using corresponding starting materials.

5

Table 9

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.              |
|-------------------------|--------------------|------|--------------------------------------|
| 103                     |                    | 2HCl | Powder<br>MS·APCI (m/z) : 338 (M+H)+ |
| 104                     |                    | 2HCl | Powder<br>MS·APCI (m/z) : 296 (M+H)+ |

Preparation example 105

- 10 A mixture of 5-amino-2-(4-fluorophenyl)-4-phenylimidazole (1.00 g) and ethyl formate (10 ml) was refluxed for 15 hours. After cooling, the reaction mixture was concentrated under reduced pressure and crystallized from diethyl ether to obtain 5-formylamino-2-(4-fluorophenyl)-4-phenylimidazole (1.17 g)  
 15 as colorless crystal.  
 Melting point: 245 to 247°C  
 MS·APCI (m/z) : 282 (MH+)

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Preparation example 106

A mixture of 5-methylamino-2-(4-fluorophenyl)-4-phenylimidazole (560 mg) in ethyl formate (20 ml) was refluxed overnight.

- 5 After cooling, the reaction mixture was concentrated under reduced pressure and crystallized from diethyl ether-hexane to obtain 5-formylmethylamino-2-(4-fluorophenyl)-4-phenylimidazole (480 mg) as colorless crystal.  
Melting point: 256 to 258°C  
10 MS·APCI (m/z): 296 (MH<sup>+</sup>)

Preparation example 107

To a solution of

- 15 5-formylamino-2-(4-fluorophenyl)-4-phenylimidazole (1.06 g) in tetrahydrofuran (15 ml) was added dropwise 10M borane·dimethylsulfide complex (1.90 ml), and the mixture was stirred under argon atmosphere at room temperature for 2.5 hours. To the reaction mixture was slowly added 10% hydrochloric acid,  
20 and the mixture was refluxed for one hour. After cooling, the mixture was neutralized by adding a saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under  
25 reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: hexane : ethyl acetate=5:1) to obtain 5-methylamino-2-(4-fluorophenyl)-4-phenylimidazole (702 mg) as colorless powder. 88 mg of the product was treated with hydrogen chloride-methanol solution  
30 to obtain the hydrochloride salt (84 mg) as colorless powder.  
Melting point: 253 to 255°C  
MS·APCI (m/z): 268 (MH<sup>+</sup>)

Preparation example 108

- 35 To a solution of 5-formylmethylamino-2-(4-fluorophenyl)-

- 67 -

4-phenylimidazole (200 mg) in tetrahydrofuran (5 ml) was added dropwise 10M borane-dimethylsulfide complex (0.34 ml), and the mixture was stirred under argon atmosphere at room temperature for overnight. To the reaction mixture was slowly added 10% hydrochloric acid, and the mixture was refluxed for one hour. After cooling, the mixture was neutralized by adding a saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: hexane : ethyl acetate=5:1), and then, treated with hydrogen chloride-methanol solution to obtain 5-dimethylamino-2-(4-fluorophenyl)-4-phenylimidazole hydrochloride (174 mg) as colorless powder.

MS·APCI (m/z): 282 (MH<sup>+</sup>)

#### Preparation example 109

To a solution of 5-amino-2-(4-fluorophenyl)-4-phenylimidazole (63 mg) and pyridine (40 mg) in methylene chloride (5 ml) was added methyl chlorocarbonate (28 mg) under ice-cooling and the mixture was stirred at room temperature overnight. To the reaction mixture was added diethyl ether, and the solvent was removed under reduced pressure. The resulting residue was triturated with diethyl ether and the powder was collected by filtration. The powder was treated with hydrogen chloride-methanol solution to obtain 5-methoxycarbonylamino-2-(4-fluorophenyl)-4-phenylimidazole hydrochloride (67 mg) as colorless powder.

MS·APCI (m/z): 312 (MH<sup>+</sup>)

#### Preparation example 110

To a solution of 5-acetylamino-2-(4-fluorophenyl)-4-phenylimidazole (142 mg) in tetrahydrofuran (7 ml) was added 10M

- 68 -

borane-tetrahydrofuran complex (12 ml, tetrahydrofuran solution), and the mixture was stirred under argon atmosphere at room temperature for 2 days. To the reaction mixture was slowly added 10% hydrochloric acid, and the mixture was stirred 5 at 60°C for 10 minutes. After cooling, the mixture was neutralized by adding a saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under 10 reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: hexane : ethyl acetate=1:2), and then, treated with hydrogen chloride-methanol solution to obtain 5-ethylamino-2-(4-fluorophenyl)-4-phenylimidazole hydrochloride (89 mg) as colorless powder.

15 MS·APCI (m/z) : 282 (MH+)

#### Preparation example 111

A mixture of 5-ethylamino-2-(4-fluorophenyl)-4-phenylimidazole (145 mg) in ethyl formate (8 ml) was refluxed for 8 hours. After cooling, the mixture was concentrated under reduced pressure, and crystallized from diethyl ether to obtain 5-formylethylamino-2-(4-fluorophenyl)-4-phenylimidazole (136 mg) as colorless crystal.

25 Melting point: 201 to 202°C  
MS·APCI (m/z) : 310 (MH+)

#### Preparation example 112

30 A mixture of 2-(5-chlorothiophen-2-yl)-4-(3-pyridyl)imidazole (1.07 g), 35% formalin aqueous solution (35 ml), potassium carbonate (1.70 g), isopropanol (30 ml) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 2 hours. After cooling, water was added to the mixture and precipitated solid was 35 collected by filtration. The solid was dissolved in methanol and, after removing insolubles by filtration, the solvent was

- 69 -

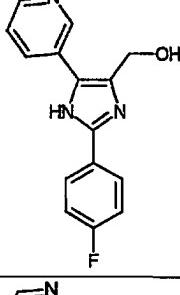
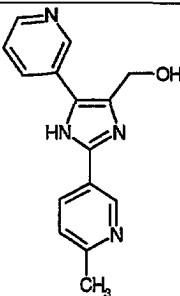
removed under reduced pressure. The resulting residue was triturated with ethyl acetate to obtain 2-(5-chlorothiophen-2-yl)-5-hydroxymethyl-4-(3-pyridyl)imidazole (519 mg) as colorless powder.

5 MS·APCI (m/z) : 292/294 (MH<sup>+</sup>)

#### Preparation examples 113 and 118

The following compounds shown in Table 10 were prepared in a  
10 manner similar to Preparation example 112 by using corresponding starting materials.

Table 10

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.   |
|-------------------------|---|---------------|---|
| 113                     |   | Free material | Crystal<br>Melting point:<br>225-228°C<br>MS·APCI (m/z) :<br>270 (M+H) <sup>+</sup> |
| 114                     |  | 3HCl          | Crystal<br>Melting point:<br>266-269°C<br>MS·APCI (m/z) :<br>267 (M+H) <sup>+</sup> |

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Table 10 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.   |
|-------------------------|--------------------|---------------|---|
| 115                     |                    | Free material | Crystal<br>Melting point:<br>232-234 °C<br>MS·APCI (m/z) :<br>269 (M+H) + |
| 116                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>277 (M+H) +                                  |
| 117                     |                    | Free material | Crystal<br>Melting point:<br>240-243 °C<br>MS·APCI (m/z) :<br>269 (M+H) + |

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Table 10 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                             |
|-------------------------|--------------------|---------------|---|
| 118                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>276 (M+H) <sup>+</sup> |

## Preparation example 119

5

To a solution of 2-(5-chlorothiophen-2-yl)-5-hydroxy-methyl-4-(3-pyridyl)imidazole (200 mg) in methylene chloride (5 ml) was added thionyl chloride (5ml), and the mixture was refluxed for one hour. After cooling, the reaction mixture was

10 concentrated under reduced pressure to obtain a crude product of 2-(5-chlorothiophen-2-yl)-5-chloromethyl-4-(3-pyridyl)-imidazole dihydrochloride (260 mg) as yellowish powder.

## Preparation example 120

15

In methanol (10 ml) was dissolved a crude product of 2-(5-chlorothiophen-2-yl)-5-chloromethyl-4-(3-pyridyl)-imidazole dihydrochloride (260 mg) and the mixture was refluxed for 2 hours. After cooling, a saturated aqueous sodium hydrogen

20 carbonate solution was added to the reaction mixture, and the mixture was extracted with a mixed solution of ethyl acetate-tetrahydrofuran. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by

25 silica gel column chromatography (solvent: chloroform :

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methanol=40:1), and then, treated with hydrogen chloride-dioxane solution to obtain 2-(5-chlorothiophen-2-yl)-5-methoxymethyl-4-(3-pyridyl)imidazole dihydrochloride (63 mg) as pale yellowish powder.

- 5 Melting point: 245 to 248°C (decomposed)  
MS·APCI (m/z): 306/308 (MH<sup>+</sup>)

Preparation examples 121 to 128

- 10 The following compounds shown in Table 11 were prepared in a manner similar to Preparation example 112 or 120 by using corresponding starting materials.

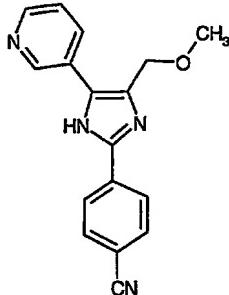
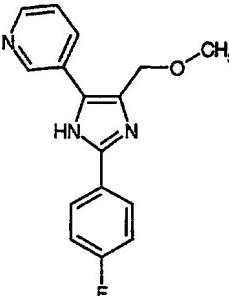
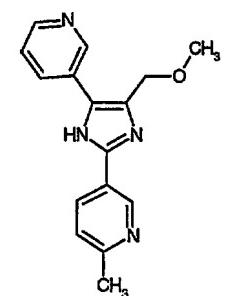
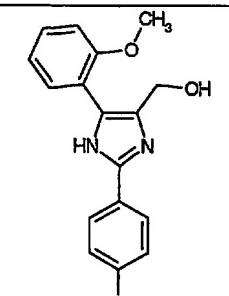
- 73 -

Table 11

| Preparation example No. | Chemical structure | Salt | Physical property, etc.   |
|-------------------------|--------------------|------|---|
| 121                     |                    | 1HCl | Crystal<br>Melting point:<br>204-207°C<br>MS APCI (m/z) :<br>283 (M+H) +  |
| 122                     |                    | 1HCl | Powder<br>MS ·APCI (m/z) :<br>289 (M+H) +                                 |
| 123                     |                    | 1HCl | Crystal<br>Melting point:<br>185-188°C<br>MS ·APCI (m/z) :<br>283 (M+H) + |
| 124                     |                    | 1HCl | Powder<br>MS ·APCI (m/z) :<br>290 (M+H) +                                 |

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Table 11 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.   |
|-------------------------|---|------|---|
| 125                     |    | 2HCl | Powder<br>MS·APCI (m/z) :<br>291 (M+H) +                                  |
| 126                     |   | 2HCl | Powder<br>MS·APCI (m/z) :<br>284 (M+H) +                                  |
| 127                     |  | 3HCl | Crystal<br>Melting point:<br>251-255 °C<br>MS·APCI (m/z) :<br>281 (M+H) + |
| 128                     |  | 1HCl | Powder<br>MS·APCI (m/z) : 299 (M+H) +                                     |

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Preparation example 129

To a solution of 2-(3-fluorophenyl)-5-hydroxymethyl-4-(3-pyridyl)imidazole (389 mg) in methylene chloride (10 ml) was  
5 added thionyl chloride (10 ml), and the mixture was refluxed for one hour. After cooling, the reaction mixture was concentrated under reduced pressure to obtain a crude product of 2-(3-fluorophenyl)-5-chloromethyl-4-(3-pyridyl)imidazole dihydrochloride (508 mg) as colorless powder.

10

Preparation example 130

To a suspension of a crude product of 2-(3-fluorophenyl)-5-chloromethyl-4-(3-pyridyl)imidazole dihydrochloride (268 mg) in tetrahydrofuran (10 ml) were added 15% aqueous sodium methyl sulfide solution (0.95 ml) and triethylamine (206 mg), and the mixture was stirred at room temperature for 1.5 hours. Water was added to the reaction mixture, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed  
15 with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : methanol=19:1) to obtain 2-(3-fluorophenyl)-5-methylthiomethyl-4-(3-pyridyl)imidazole  
20 (198 mg) as colorless powder.

25

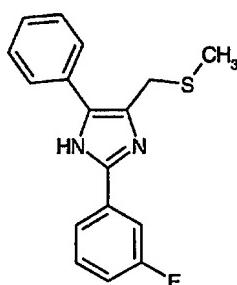
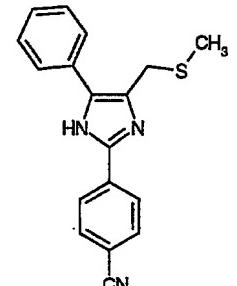
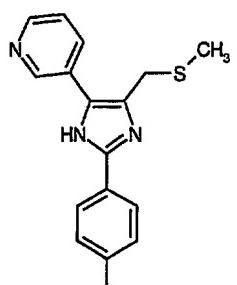
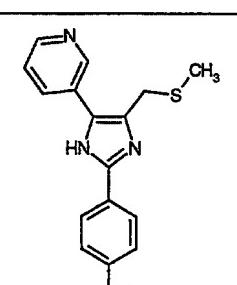
MS·APCI (m/z): 300 (MH<sup>+</sup>)

Preparation examples 131 to 134

30 The following compounds shown in Table 12 were prepared in a manner similar to Preparation example 130 by using corresponding starting materials.

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Table 12

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.  |
|-------------------------|---|---------------|--|
| 131                     |    | 1HCl          | Crystal<br>Melting point:<br>218-220°C<br>MS·APCI (m/z) :<br>299 (M+H) + |
| 132                     |   | 1HCl          | Crystal<br>Melting point:<br>256-259°C<br>MS·APCI (m/z) :<br>306 (M+H) + |
| 133                     |  | Free material | Crystal<br>Melting point:<br>172-174°C<br>MS·APCI (m/z) :<br>300 (M+H) + |
| 134                     |  | Free material | Crystal<br>Melting point:<br>209-211°C<br>MS·APCI (m/z) :<br>307 (M+H) + |

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Preparation example 135

To a solution of 2-(3-fluorophenyl)-5-methylthiomethyl-4-(3-pyridyl)imidazole (152 mg) in tetrahydrofuran (10 ml) was  
5 added metachloroperbenzoic acid (97 mg, 70% purity) under ice-cooling, and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with  
10 brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : methanol = 19:1), and then, treated with hydrogen chloride-dioxane solution to obtain 2-(3-fluorophenyl)-5-  
15 methylsulfinylmethyl-4-(3-pyridyl)imidazole (140 mg) as colorless powder.

MS·APCI (m/z): 316 (MH<sup>+</sup>)

Preparation examples 136 to 140

20

The following compounds shown in Table 13 were prepared in a manner similar to Preparation example 135 by using corresponding starting materials.

25

Table 13

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.   |
|-------------------------|--------------------|------|---|
| 136                     |                    | 1HCl | Crystal<br>Melting point:<br>198-200°C<br>MS·APCI (m/z) :<br>315 (M+H)+ |
| 137                     |                    | 1HCl | Powder<br>MS·APCI (m/z) :<br>322 (M+H)+                                 |
| 138                     |                    | 2HCl | Powder<br>MS·APCI (m/z) :<br>316 (M+H)+                                 |
| 139                     |                    | 2HCl | Powder<br>MS·APCI (m/z) :<br>323 (M+H)+                                 |

Table 13 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.   |
|-------------------------|--------------------|------|---|
| 140                     |                    | 1HCl | Crystal<br>Melting point:<br>278-280°C<br>MS·APCI (m/z) :<br>351 (M+H)+ |

## Preparation example 141

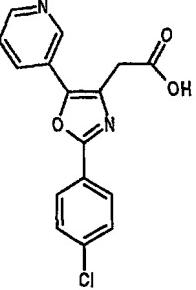
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- A mixture of ethyl 2-(5-chlorothiophen-2-yl)-5-(3-pyridyl)oxazole-4-yl acetate (68 mg), lithium hydroxide (9 mg), ethanol (4 ml) and water (4 ml) was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, acidified to pH 4 with 10% hydrochloric acid, and precipitated solid was collected by filtration. This solid was treated with hydrogen chloride-dioxane solution to obtain 2-(5-chlorothiophen-2-yl)-5-(3-pyridyl)oxazole-4-yl acetic acid hydrochloride (50 mg) as pale yellowish powder.
- 10 Melting point: 234 to 238°C (decomposed)  
 15 MS·APCI (m/z) : 321/323 (MH+)

## Preparation example 142

- 20 The following compounds shown in Table 14 were prepared in a manner similar to Preparation example 141 by using corresponding starting materials.

Table 14

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                |
|-------------------------|---|------|--|
| 142                     |  | 1HCl | Powder<br>MS·APCI (m/z) :<br>313 (M-H) |

## Preparation examples 143 and 144

- 5 Amixture of 2-(5-chlorothiophen-3-yl)-5-ethyl-4-(3-pyridyl)-imidazole (2.00 g) in chlorosulfonic acid (15 ml) was stirred at room temperature for one week. The mixture was slowly added dropwise to 28% aqueous ammonia (500 ml), and the resulting mixture was stirred for 30 minutes and then concentrated under reduced pressure. The resulting residue was dissolved in methanol-tetrahydrofuran (5:1), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel flush column chromatography (solvent: chloroform : methanol=10:1 → 2.5:1), and then, by NH silica gel flush column chromatography (solvent: chloroform : methanol=10:1 → 4:1) to obtain 2-(5-chloro-2-sulfothiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole and 2-(5-chloro-2-sulfamoylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole.
- 10 15 Each product was treated with hydrogen chloride-dioxane solution to obtain 2-(5-chloro-2-sulfothiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole dihydrochloride (741 mg) and 2-(5-chloro-2-sulfamoylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole dihydrochloride (105 mg) each as colorless powder.
- 20 25 2-(5-Chloro-2-sulfothiophen-3-yl)-5-ethyl-4-(3-pyridyl)-

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imidazole dihydrochloride (Preparation example 143)  
ESI·MS (m/z): 368 (M-H)

2-(5-Chloro-2-sulfamoylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)  
5 imidazole dihydrochloride (Preparation example 144)  
MS·APCI (m/z): 369 (MH+)

Preparation example 145

10 To a solution of 2-(2-ethoxycarbonylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole (879 mg) in tetrahydrofuran (20 ml) was added lithium aluminum hydride (204 mg) under ice-cooling, and the mixture was stirred under argon atmosphere at the same temperature for 1.5 hours. Under ice-cooling, an aqueous  
15 potassium sodium tartarate solution and ethyl acetate were added to the mixture and the organic layer was collected. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel  
20 column chromatography (solvent: chloroform : methanol=19:1), and then, treated with hydrogen chloride-ethanol solution to obtain 2-(2-hydroxymethylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole dihydrochloride (788 mg) as colorless powder.  
MS·APCI (m/z): 286 (MH+)

25

Preparation example 146

To a solution of ethyl 2-(5-chlorothiophen-2-yl)-4-(3-pyridyl)imidazol-5-yl acetate (122 mg) in tetrahydrofuran (3.5 ml) was added lithium aluminum hydride (15 mg) under ice-cooling, and the mixture was stirred under ice-cooling for 2.5 hours. Under ice-cooling, an aqueous sodium hydroxide solution and ethyl acetate were added to the mixture, and the organic layer was collected. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by

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preparative thin-layer chromatography (TLC) (silica gel; solvent: chloroform : methanol=20:1) to obtain 2-(5-chlorothiophen-2-yl)-5-hydroxyethyl-4-(3-pyridyl)imidazole (109 mg) as colorless crystalline powder. 27 mg of the product was  
5 treated with hydrogen chloride-dioxane solution to obtain the dihydrochloride salt (26 mg) as colorless powder.  
Melting point: 179 to 180°C (free material)  
MS·APCI (m/z): 306 (MH<sup>+</sup>) (hydrochloride)

10 Preparation example 147

A mixture of ethyl 4-(4-fluorobenzoylamino)-4-(2-thienyl)-3-ketobutyrate (349 mg), and phosphorus oxychloride (0.12 ml) in N,N-dimethylformamide (5 ml) was stirred at room temperature  
15 for 2.5 hours. The reaction mixture was poured into water, neutralized with a saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The  
20 resulting residue was purified by silica gel flush column chromatography (solvent: hexane : ethyl acetate=20:1) to obtain ethyl 2-(4-fluorophenyl)-4-(2-thienyl)oxazol-5-yl acetate (95 mg) as pale yellowish powder.  
MS·APCI (m/z): 332 (MH<sup>+</sup>)

25

Preparation example 148

To a solution of ethyl 2-(4-fluorophenyl)-4-(2-thienyl)-oxazol-5-yl acetate (94 mg) in tetrahydrofuran (3 ml) and ethanol  
30 (3 ml) was added 1N aqueous sodium hydroxide solution (1 ml) and the mixture was stirred at room temperature for one hour. To the reaction mixture was added 10% hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and  
35 the solvent was removed under reduced pressure. The resulting residue was dissolved in methanol (5 ml), 0.5M sodium methoxide

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(556 µl, methanol solution) was added to the solution and the solvent was removed under reduced pressure to obtain sodium 2-(4-fluorophenyl)-4-(2-thienyl)oxazol-5-yl acetate (90 mg) as pale brownish powder.

5 ESI·MS (m/z) : 302 (M-H)

Preparation example 149

To a solution of ethyl 2-(4-fluorophenyl)oxazol-4-yl acetate (11.10 g) in chloroform (110 ml) was added bromine (2.47 ml) at room temperature and the mixture was stirred at room temperature for one hour. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium thiosulfate solution, and the organic layer was collected. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was crystallized from hexane-diethyl ether to obtain ethyl 5-bromo-2-(4-fluorophenyl)oxazol-4-yl acetate (7.47 g) as colorless crystal. Further, the filtrate was purified by silica gel flush column chromatography (solvent: n-hexane : ethyl acetate=10:1) to obtain ethyl 5-bromo-2-(4-fluorophenyl)-oxazol-4-yl acetate (3.57 g) as pale yellowish crystal.

Melting point: 84 to 85°C

25 MS·APCI (m/z) : 323/330 (MH+)

Preparation example 150

A mixture of ethyl 2-(4-fluorophenyl)oxazol-4-yl acetate (249 mg), iodine (127 mg) and [bis(trifluoroacetoxy)]iodobenzene (244 mg) in chloroform (3 ml) was stirred at room temperature for 4 hours. To the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium thiosulfate solution, and the organic layer was collected. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under

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reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: n-hexane : ethyl acetate=8:1) to obtain ethyl 2-(4-fluorophenyl)-5-iodoxazol-4-yl acetate (300 mg) as colorless crystal.

5 Melting point: 120 to 122°C

MS·APCI (m/z): 376 (MH<sup>+</sup>)

Preparation example 151

10 A mixture of ethyl 5-bromo-2-(4-fluorophenyl)oxazol-4-yl acetate (328 mg), 5-chlorothiophen-2-boric acid (244 mg), bis(triphenylphosphine)palladium (II) dichloride (35 mg) in 2M aqueous sodium carbonate solution (1.5 ml) and dimethoxyethane (5 ml) was refluxed for one hour. After cooling, to the reaction  
15 mixture were added water and ethyl acetate, the organic layer was collected, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel flush column chromatography (solvent: n-hexane : ethyl acetate=6:1) to obtain ethyl  
20 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-4-yl acetate (181 mg) as pale yellowish crystal.

Melting point: 129 to 130°C

MS·APCI (m/z): 366/368 (MH<sup>+</sup>)

25 Preparation example 152

To a solution of ethyl 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-4-yl acetate (115 mg) in methanol (5 ml) was added 4N aqueous sodium hydroxide solution (1 ml), and the  
30 mixture was refluxed for 30 minutes. After cooling, ethyl acetate and 10% hydrochloric acid were added to the reaction mixture, and the organic layer was collected. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting  
35 residue was dissolved in methanol (5 ml), 0.5M sodium methoxide (605 µl, methanol solution) was added to the solution and the

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solvent was removed under reduced pressure. The resulting residue was triturated with acetone to obtain 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-4-yl acetic acid sodium salt (100 mg) as pale yellowish powder.

5 ESI·MS (m/z): 336 (M-H)

Preparation examples 153 to 166

10 The following compounds shown in Table 15 were prepared in a manner similar to Preparation example 63, 151 or 152 by using corresponding starting materials.

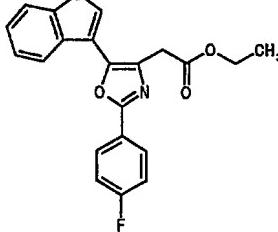
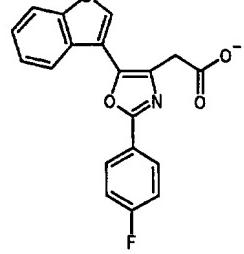
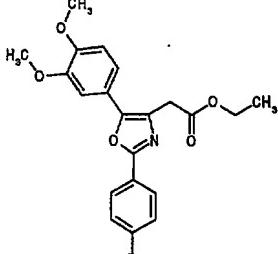
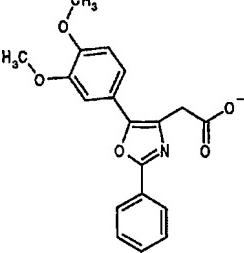
- 86 -

Table 15

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.   |
|-------------------------|--------------------|---------------|---|
| 153                     |                    | Na            | Crystal<br>Melting point:<br><300°C<br>MS·APCI (m/z) :<br>296 (M-Na)  |
| 154                     |                    | Free material | Crystal<br>Melting point: 105-107°C<br>MS·APCI (m/z) :<br>344 (M+H) + |
| 155                     |                    | Na            | Powder<br>ESI·MS (m/z) :<br>314 (M-Na)                                |
| ~156                    |                    | Na            | Powder<br>ESI·MS (m/z) :<br>298 (M-Na)                                |

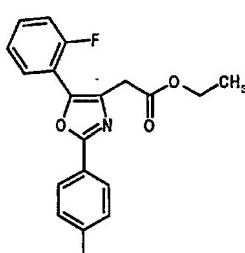
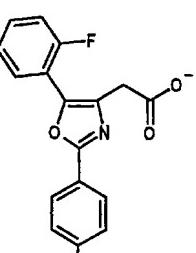
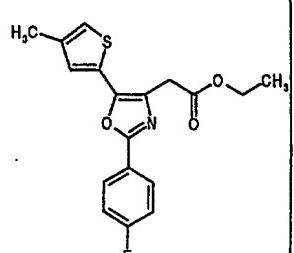
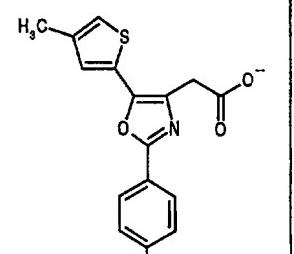
- 87 -

Table 15 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.               |
|-------------------------|---|---------------|---------------------------------------|
| 157                     |    | Free material | Powder<br>MS·APCI (m/z) : 382 (M+H) + |
| 158                     |   | Na            | Powder<br>MS·APCI (m/z) : 352 (M-Na)  |
| 159                     |  | Free material | Powder<br>MS·APCI (m/z) : 386 (M+H) + |
| 160                     |  | Na            | Powder<br>MS·APCI (m/z) : 356 (M-Na)  |

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Table 15 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.  |
|-------------------------|---|---------------|--|
| 161                     |    | Free material | Crystal<br>Melting point:<br>88-89°C<br>MS·APCI (m/z) :<br>344 (M+H) +   |
| 162                     |    | Na            | Powder<br>MS·APCI (m/z) :<br>314 (M-Na)                                  |
| 163                     |  | Free material | Crystal<br>Melting point:<br>138-139°C<br>MS·APCI (m/z) :<br>346 (M+H) + |
| 164                     |  | Na            | Powder<br>MS·APCI (m/z) :<br>316 (M-Na)                                  |

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Table 15 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.               |
|-------------------------|--------------------|---------------|---------------------------------------|
| 165                     |                    | Free material | Powder<br>MS·APCI (m/z) : 362 (M+H) + |
| 166                     |                    | Na            | Powder<br>MS·APCI (m/z) : 332 (M-Na)  |

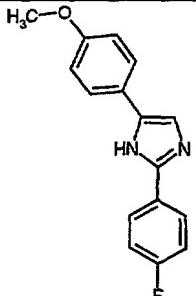
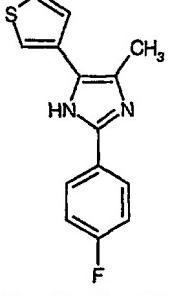
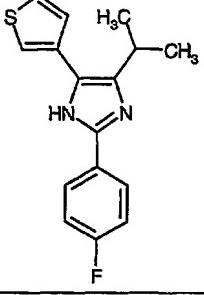
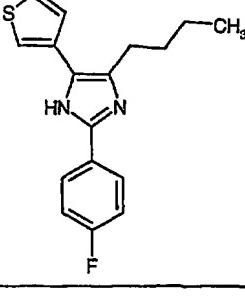
## Preparation examples 167 to 202

5

The following compounds shown in Table 16 were prepared in a manner similar to one of the above-mentioned Preparation examples, or conventionally known preparation processes as described in Japanese Provisional Patent Publications No. 5832/1972, No. 10 29771/1973 and the like.

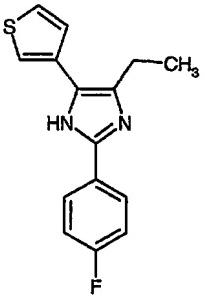
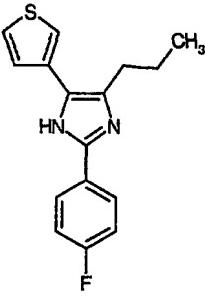
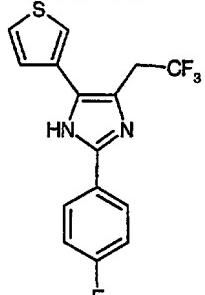
- 90 -

Table 16

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc. |
|-------------------------|---|---------------|-------------------------|
| 167                     |    | Free material | MS·EI (m/z) : 268 (M+)  |
| 168                     |   | Free material | MS·EI (m/z) : 258 (M+)  |
| 169                     |  | Free material | MS·EI (m/z) : 286 (M+)  |
| 170                     |  | Free material |                         |

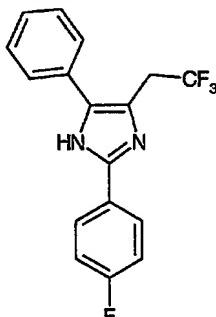
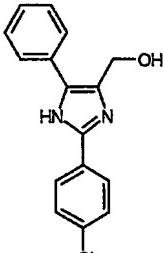
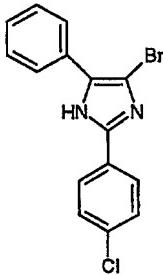
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Table 16 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc. |
|-------------------------|---|---------------|-------------------------|
| 171                     |    | Free material | MS·EI (m/z) : 272 (M+)  |
| 172                     |   | Free material | MS·EI (m/z) : 286 (M+)  |
| 173                     |  | Free material | MS·EI (m/z) : 326 (M+)  |
| 174                     |  | Free material | MS·EI (m/z) : 252 (M+)  |

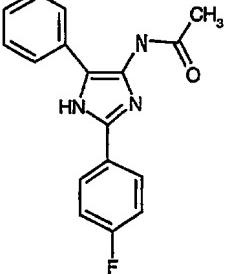
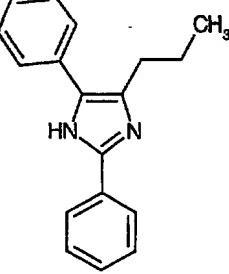
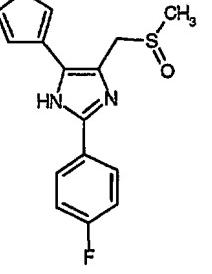
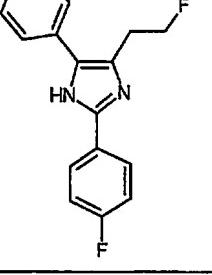
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Table 16 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.              |
|-------------------------|---|---------------|--------------------------------------|
| 175                     |    | Free material | MS·EI (m/z) : 320 (M+)               |
| 176                     |   | Free material |                                      |
| 177                     |  | Free material | MS·EI (m/z) : 332/334/336 (M+)       |
| 178                     |  | 2HCl          | Powder<br>MS APCI (m/z) : 254 (M+H)+ |

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Table 16 (contd.)

| Preparation example No.. | Chemical structure  | Salt | Physical property, etc.               |
|--------------------------|---|------|---------------------------------------|
| 179                      |    | 1HCl | Powder<br>MS APCI (m/z) : 296 (M+H) + |
| 180                      |   | 1HCl | Powder<br>MS APCI (m/z) : 263 (M+H) + |
| 181                      |  | 1HCl | Powder<br>MS APCI (m/z) : 321 (M+H) + |
| 182                      |  | 1HCl | Powder<br>MS APCI (m/z) : 285 (M+H) + |

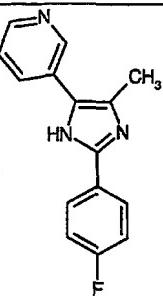
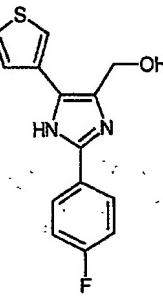
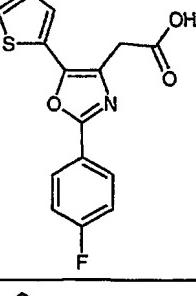
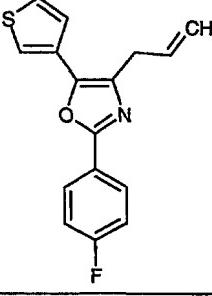
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Table 16 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.               |
|-------------------------|--------------------|------|---------------------------------------|
| 183                     |                    | 1HCl | Powder<br>MS APCI (m/z) : 329 (M+H) + |
| 184                     |                    | 1HCl | Powder<br>MS APCI (m/z) : 343 (M+H) + |
| 185                     |                    | 1HCl | Powder<br>MS APCI (m/z) : 345 (M+H) + |
| 186                     |                    | 1HCl | Powder<br>MS APCI (m/z) : 345 (M+H) + |

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Table 16 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.               |
|-------------------------|---|---------------|---------------------------------------|
| 187                     |    | 2HCl          | Powder<br>MS APCI (m/z) : 254 (M+H) + |
| 188                     |   | Free material |                                       |
| 189                     |  | Free material | Crystal<br>Melting point: 208-209°C   |
| 190                     |  | Free material | Powder<br>MS EI (m/z) : 285 (M+)      |

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Table 16 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.   |
|-------------------------|--------------------|---------------|---|
| 191                     |                    | Free material | Crystal<br>Melting point:<br>109-111°C<br>MS·APCI (m/z) :<br>332 (M+H)+ |
| 192                     |                    | Free material | Crystal<br>Melting point:<br>214-215°C                                  |
| 193                     |                    | Free material |   |
| 194                     |                    | Free material | Powder<br>MS EI (m/z) :<br>319/321 (M+)                                 |

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Table 16 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.  |
|-------------------------|--------------------|---------------|--|
| 195                     |                    | Free material | MS EI(m/z) : 334/336(M+)   |
| 196                     |                    | Free material | Crystal<br>Melting point:<br>125-127°C<br>MS·APCI(m/z) : 328 (M+H) + |
| 197                     |                    | Na            | Powder<br>MS·ESI(m/z) : 302 (M-Na)                                   |

Table 16 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.                 |
|-------------------------|--------------------|---------------|---|
| 198                     |                    | Na            | Powder<br>MS·ESI (m/z) :<br>298 (M-Na)  |
| 199                     |                    | Na            | Powder<br>MS·ESI (m/z) :<br>314 (M-Na)  |
| 200                     |                    | Free material | Crystal<br>Melting point:<br>198-199°C  |
| 201                     |                    | Na            | Powder<br>MS·APCI (m/z) :<br>302 (M-Na) |

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Table 16 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.  |
|-------------------------|--------------------|---------------|--|
| 202                     |                    | Free material | Crystal<br>Melting point:<br>123-125°C<br>MS·APCI(m/z):<br>327(M+H)+ |

## Preparation example 203

5

A mixture of ethyl 3-amino-4-(5-chlorothiophen-2-yl)-4-oxobutyrate hydrochloride (300 mg), benzo[b]furan-5-carboxylic acid (245 mg), 3-ethyl-1-(3-dimethylamino-propyl)carbodiimide hydrochloride (289 mg), 1-hydroxybenzotriazole (204 mg) and triethylamine (0.35 ml) in methylene chloride (4.5 ml) was stirred at room temperature for overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=4:1), and then, triturated with diisopropyl ether to obtain ethyl 3-[(5-benzo[b]furoyl)amino-4-(5-chlorothiophen-2-yl)-4-oxo-butylate (352 mg) as colorless powder.

To a solution of the resulting ethyl 3-[(5-benzo[b]furoyl)amino-4-(5-chlorothiophen-2-yl)-4-oxobutyrate (331 mg) in N,N-dimethylformamide (4.08 ml) was added phosphoryl chloride (0.23 ml) under ice-cooling, and the mixture was stirred at 60°C overnight. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, the mixture was extracted

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with ethyl acetate, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : ethyl acetate= 20:1), and then, 5 triturated with diisopropyl ether to obtain ethyl 2-(5-benzo[b]furyl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (257 mg) as colorless powder.

MS·APCI (m/z): 388/390 (MH<sup>+</sup>)

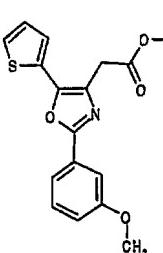
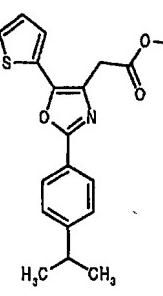
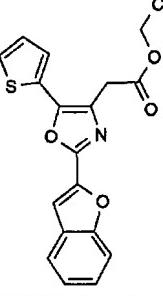
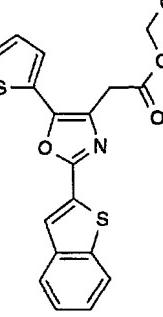
10 Preparation examples 204 to 226

The following compounds shown in Table 17 were prepared in a manner similar to Preparation example 203 by using corresponding starting materials.

15

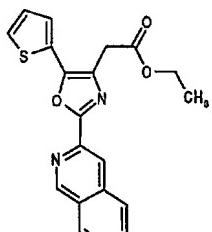
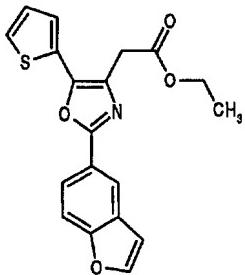
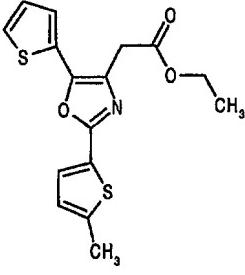
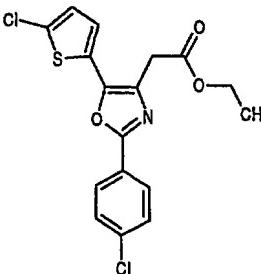
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Table 17

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.                 |
|-------------------------|---|---------------|---|
| 204                     |    | Free material | Powder<br>MS·APCI (m/z) :<br>344 (M+H)+ |
| 205                     |   | Free material | Powder<br>MS·APCI (m/z) :<br>356 (M+H)+ |
| 206                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>354 (M+H)+ |
| 207                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>370 (M+H)+ |

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Table 17 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.                   |
|-------------------------|---|---------------|---|
| 208                     |    | Free material | Powder<br>MS·APCI (m/z) : 365 (M+H) +     |
| 209                     |   | Free material | Powder<br>MS·APCI (m/z) : 354 (M+H) +     |
| 210                     |  | Free material | Powder<br>MS·APCI (m/z) : 334 (M+H) +     |
| 211                     |  | Free material | Powder<br>MS·APCI (m/z) : 382/384 (M+H) + |

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Table 17 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.                   |
|-------------------------|--------------------|---------------|---|
| 212                     |                    | Free material | Powder<br>MS·APCI (m/z) : 355/357 (M+H) + |
| 213                     |                    | Free material | Powder<br>MS·APCI (m/z) : 348 (M+H) +     |
| 214                     |                    | Free material | Powder<br>MS·APCI (m/z) : 412 (M+H) +     |
| 215                     |                    | Free material | Powder<br>MS·APCI (m/z) : 404/406 (M+H) + |

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Table 17 (contd.)

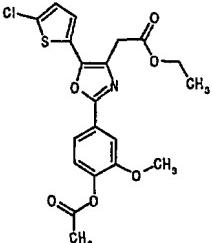
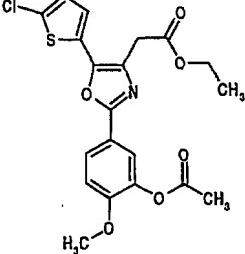
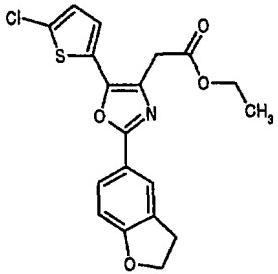
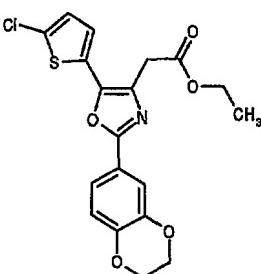
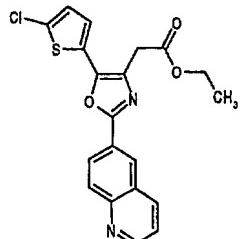
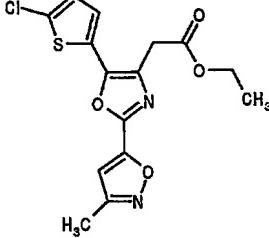
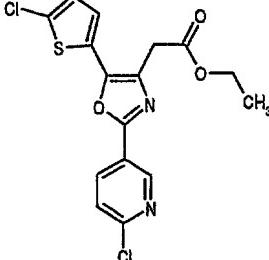
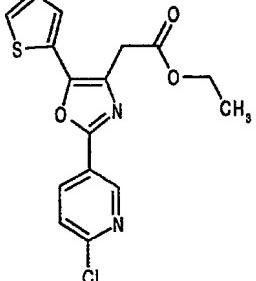
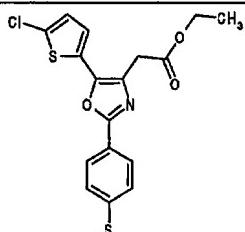
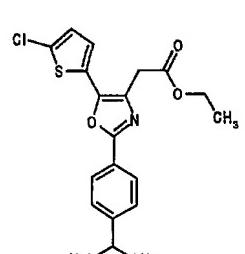
| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.                   |
|-------------------------|---|---------------|---|
| 216                     |    | Free material | Powder<br>MS·APCI (m/z) : 436/438 (M+H) + |
| 217                     |   | Free material | Powder<br>MS·APCI (m/z) : 436/438 (M+H) + |
| 218                     |  | Free material | Powder<br>MS·APCI (m/z) : 390/392 (M+H) + |
| 219                     |  | Free material | Powder<br>MS·APCI (m/z) : 406/408 (M+H) + |

Table 17 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.                   |
|-------------------------|---|---------------|---|
| 220                     |    | Free material | Powder<br>MS·APCI (m/z) : 399/401 (M+H) + |
| 221                     |   | Free material | Powder<br>MS·APCI (m/z) : 353/355 (M+H) + |
| 222                     |  | Free material | Powder<br>MS·APCI (m/z) : 383/385 (M+H) + |
| 223                     |  | Free material | Powder<br>MS·APCI (m/z) : 349/351 (M+H) + |

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Table 17 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 224                     |    | Free material | Powder<br>MS·APCI (m/z) : 372 (M+H) +     |
| 225                     |    | Free material | Powder<br>MS·APCI (m/z) : 394 (M+H) +     |
| 226                     |  | Free material | Powder<br>MS·APCI (m/z) : 392/394 (M+H) + |

## Preparation example 227

5

To a solution of 4-[(5-benzo[b]furoyl)aminoacetyl]-2-chlorothiophene (543 mg) in N,N-dimethylformamide (10 ml) was added sodium hydride (71.3 mg, 60% mineral oil) under ice-cooling, and the mixture was stirred at room temperature for 20 minutes.

- 10 After ice-cooling, ethyl bromoacetate (0.21 ml) was added dropwise to the mixture, and the resulting mixture was stirred at room temperature for 40 minutes. After cooling, 5% aqueous citric acid solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer

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was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain a crude product of ethyl 3-[ (5-benzo[b]furoyl)amino]-4-(5-chlorothiophen-3-yl)-4-oxobutyrate (896 mg).

5

To a solution of the resulting crude product of ethyl 3-[ (5-benzo[b]furoyl)amino]-4-(5-chlorothiophen-3-yl)-4-oxobutyrate (896 mg) in N,N-dimethylformamide (7 ml) was added phosphoryl chloride (0.48 ml) at room temperature, and the

10 mixture was stirred at the same temperature overnight. To the reaction mixture was added water, the mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography  
15 (solvent: hexane : acetone=7:1), and then, triturated with diethyl ether to obtain ethyl 2-(5-benzo[b]furyl)-5-(5-chlorothiophen-3-yl)oxazol-4-yl acetate (349 mg) as colorless powder.

MS·APCI (m/z): 388 (MH+)

20 Preparation examples 228 to 232

The following compounds shown in Table 18 were prepared in a manner similar to Preparation example 227 by using corresponding starting materials.

25

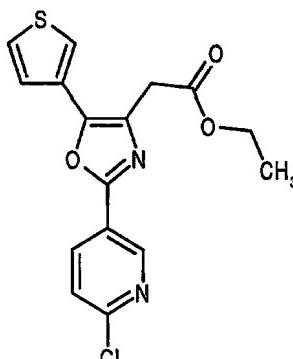
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Table 18

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.               |
|-------------------------|--------------------|---------------|---------------------------------------|
| 228                     |                    | Free material | Powder<br>MS·APCI(m/z) :<br>366(M+H)+ |
| 229                     |                    | Free material | Powder<br>MS·APCI(m/z) :<br>366(M+H)+ |
| 230                     |                    | Free material | Powder<br>MS·APCI(m/z) :<br>388(M+H)+ |
| 231                     |                    | Free material |                                       |

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Table 18 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 232                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>349/351(M+H)+ |

Preparation examples 233 to 293

5

The following compounds shown in Table 19 were prepared in a manner similar to Preparation example 148 or 152 by using corresponding starting materials.

10

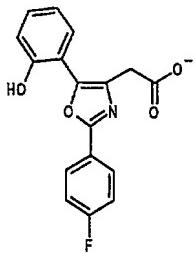
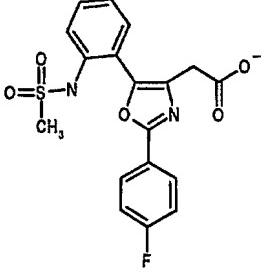
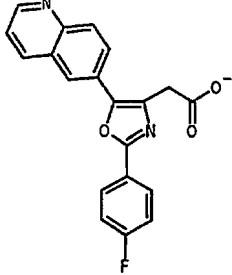
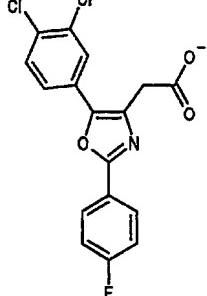
- 110 -

Table 19

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                |
|-------------------------|--------------------|------|--|
| 233                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>346 (M-Na) |
| 234                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>346 (M-Na) |
| 235                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>314 (M-Na) |
| 236                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>314 (M-Na) |

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Table 19 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical property, etc.                |
|-------------------------|---|------|--|
| 237                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>312 (M-Na) |
| 238                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>389 (M-Na) |
| 239                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>347 (M-Na) |
| 240                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>364 (M-Na) |

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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                |
|-------------------------|--------------------|------|--|
| 241                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>330 (M-Na) |
| 242                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>346 (M-Na) |
| 243                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>330 (M-Na) |
| 244                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>364 (M-Na) |

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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.             |
|-------------------------|--------------------|------|-------------------------------------|
| 245                     |                    | Na   | Powder<br>ESI·MS (m/z) : 396 (M-Na) |
| 246                     |                    | Na   | Powder<br>ESI·MS (m/z) : 344 (M-Na) |
| 247                     |                    | Na   | Powder<br>ESI·MS (m/z) : 326 (M-Na) |
| 248                     |                    | Na   | Powder<br>ESI·MS (m/z) : 338 (M-Na) |

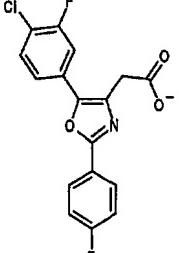
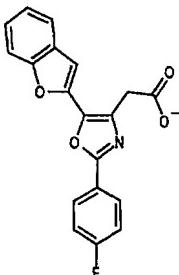
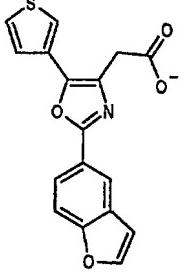
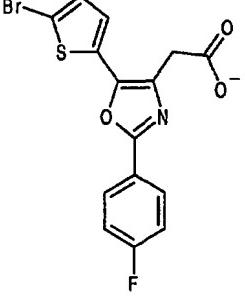
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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                |
|-------------------------|--------------------|------|--|
| 249                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>349 (M-Na) |
| 250                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>344 (M-Na) |
| 251                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>388 (M-Na) |
| 252                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>322 (M-Na) |

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Table 19 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical property, etc.                |
|-------------------------|---|------|--|
| 253                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>348 (M-Na) |
| 254                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>336 (M-Na) |
| 255                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>324 (M-Na) |
| 256                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>382 (M-Na) |

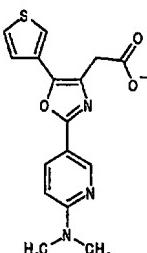
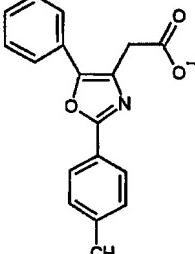
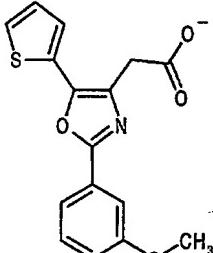
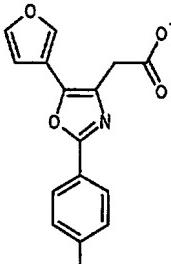
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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                 |
|-------------------------|--------------------|------|---|
| 257                     |                    | Na   | Powder<br>ESI·MS (m/z) : 350 (M-Na)     |
| 258                     |                    | Na   | Powder<br>ESI·MS (m/z) : 312 (M-Na)     |
| 259                     |                    | Na   | Powder<br>ESI·MS (m/z) : 328 (M-Na)     |
| 260                     |                    | Na   | Powder<br>ESI·MS (m/z) : 362/364 (M-Na) |

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Table 19 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical property, etc.                |
|-------------------------|---|------|--|
| 261                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>328 (M-Na) |
| 262                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>292 (M-Na) |
| 263                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>314 (M-Na) |
| 264                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>286 (M-Na) |

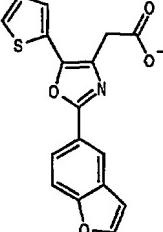
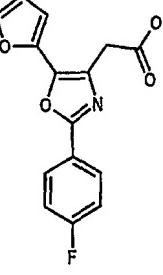
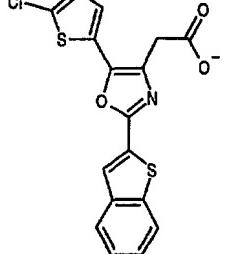
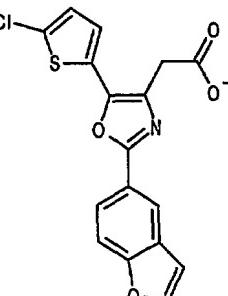
- 118 -

Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                |
|-------------------------|--------------------|------|--|
| 265                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>304 (M-Na) |
| 266                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>324 (M-Na) |
| 267                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>340 (M-Na) |
| 268                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>304 (M-Na) |

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Table 19 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical property, etc.                    |
|-------------------------|---|------|--|
| 269                     |    | Na   | Powder<br>ESI·MS (m/z) : 324 (M-Na)        |
| 270                     |   | Na   | Powder<br>ESI·MS (m/z) : 286 (M-Na)        |
| 271                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>374/376 (M-Na) |
| 272                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>358/360 (M-Na) |

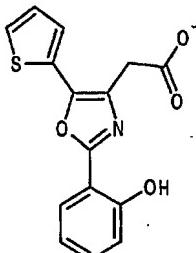
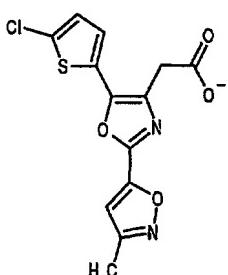
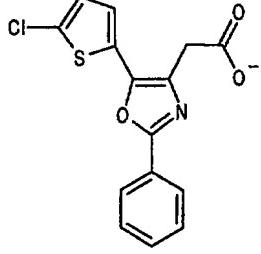
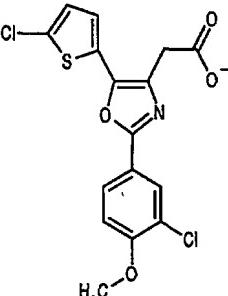
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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                 |
|-------------------------|--------------------|------|---|
| 273                     |                    | Na   | Powder<br>ESI·MS (m/z) : 360 (M-Na)     |
| 274                     |                    | Na   | Powder<br>ESI·MS (m/z) : 325 (M-Na)     |
| 275                     |                    | Na   | Powder<br>ESI·MS (m/z) : 352/354 (M-Na) |
| 276                     |                    | Na   | Powder<br>ESI·MS (m/z) : 335 (M-Na)     |

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Table 19 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical property, etc.                 |
|-------------------------|---|------|---|
| 277                     |    | Na   | Powder<br>ESI·MS (m/z) : 300 (M-Na)     |
| 278                     |   | Na   | Powder<br>ESI·MS (m/z) : 323/325 (M-Na) |
| 279                     |  | Na   | Powder<br>ESI·MS (m/z) : 318 (M-Na)     |
| 280                     |  | Na   | Powder<br>ESI·MS (m/z) : 382 (M-Na)     |

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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                 |
|-------------------------|--------------------|------|---|
| 281                     |                    | Na   | Powder<br>ESI·MS (m/z) : 364 (M-Na)     |
| 282                     |                    | Na   | Powder<br>ESI·MS (m/z) : 360/362 (M-Na) |
| 283                     |                    | Na   | Powder<br>ESI·MS (m/z) : 376/378 (M-Na) |
| 284                     |                    | Na   | Powder<br>ESI·MS (m/z) : 369/371 (M-Na) |

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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                 |
|-------------------------|--------------------|------|---|
| 285                     |                    | Na   | Powder<br>ESI·MS (m/z) : 336 (M-Na)     |
| 286                     |                    | Na   | Powder<br>ESI·MS (m/z) : 336/338 (M-Na) |
| 287                     |                    | Na   | Powder<br>ESI·MS (m/z) : 358 (M-Na)     |
| 288                     |                    | Na   | Powder<br>ESI·MS (m/z) : 358 (M-Na)     |

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Table 19 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical property, etc.                    |
|-------------------------|--------------------|------|--|
| 289                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>364/366 (M-Na) |
| 290                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>364/366 (M-Na) |
| 291                     |                    | Na   | Powder<br>ESI·MS (m/z) : 326 (M-Na)        |

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Table 19 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical property, etc.                |
|-------------------------|---|------|--|
| 292                     | <p>Chemical structure of compound 292: A benzene ring with a hydroxyl group (HO) at position 1 and a 2-(2-fluorophenyl)-5-methyl-1,3-dihydro-2H-pyrazole-4-carboxylate group at position 4.</p>             | Na   | Powder<br>ESI·MS (m/z) :<br>384 (M-Na) |
| 293                     | <p>Chemical structure of compound 293: A benzene ring with a methoxy group (OCH<sub>3</sub>) at position 1 and a 2-(2-fluorophenyl)-5-methyl-1,3-dihydro-2H-pyrazole-4-carboxylate group at position 4.</p> | Na   | Powder<br>ESI·MS (m/z) :<br>342 (M-Na) |

## Preparation examples 294 and 295

5

The following compounds shown in Table 20 were prepared in a manner similar to Preparation example 149 by using corresponding starting materials.

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Table 20

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.   |
|-------------------------|--------------------|---------------|---|
| 294                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>340/342 (M+H) +                            |
| 295                     |                    | Free material | Crystal<br>Melting point:<br>120-122°C<br>MS·APCI (m/z) :<br>376 (MH) + |

## Preparation example 296

5

A mixture of ethyl 5-bromo-2-(4-fluorophenyl)oxazol-4-yl acetate (164 mg), phenylboric acid (91 mg) and bis(tri-phenylphosphine) palladium (II) chloride (18 mg) in 2M aqueous sodium carbonate solution (0.75 ml) and dimethoxyethane (3 ml) was stirred under argon atmosphere at 100°C for one hour. After cooling, to the reaction mixture were added water and ethyl acetate, the organic layer was collected, washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=6:1) to obtain ethyl 2-(4-fluoro-

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phenyl)-5-phenyloxazol-4-yl acetate (144 mg) as colorless powder.

Melting point: 118 to 120°C

MS·APCI (m/z): 326 (MH<sup>+</sup>)

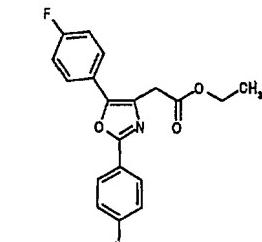
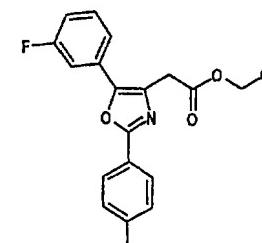
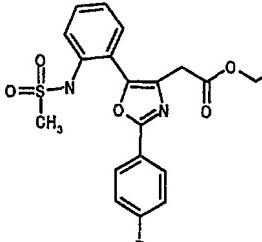
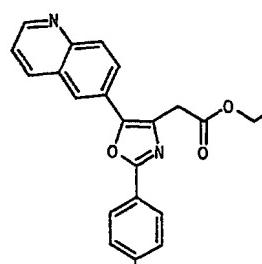
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Preparation examples 297 to 320

The following compounds shown in Table 21 were prepared in a manner similar to Preparation example 296 by using corresponding  
10 starting materials.

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Table 21

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.               |
|-------------------------|---|---------------|---------------------------------------|
| 297                     |    | Free material | Powder<br>MS·APCI (m/z) : 344 (M+H) + |
| 298                     |    | Free material | Powder<br>MS·APCI (m/z) : 344 (M+H) + |
| 299                     |  | Free material | Powder<br>MS·APCI (m/z) : 419 (M+H) + |
| 300                     |  | Free material | Powder<br>MS·APCI (m/z) : 377 (M+H) + |

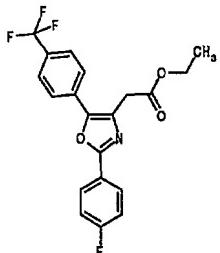
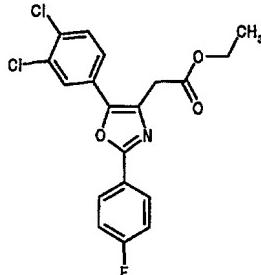
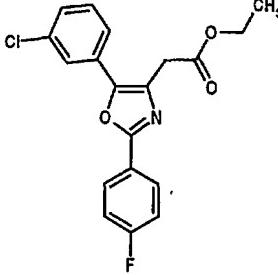
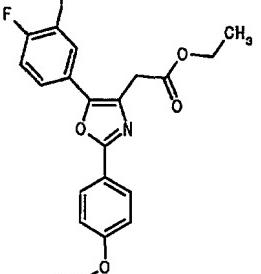
- 129 -

Table 21 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical property, etc.               |
|-------------------------|--------------------|---------------|---------------------------------------|
| 301                     |                    | Free material | Powder<br>MS·APCI (m/z) : 432 (M+H) + |
| 302                     |                    | Free material | Powder<br>MS·APCI (m/z) : 342 (M+H) + |
| 303                     |                    | Free material | Powder<br>MS·APCI (m/z) : 376 (M+H) + |
| 304                     |                    | Free material | Powder<br>MS·APCI (m/z) : 360 (M+H) + |

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Table 21 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                      |
|-------------------------|---|---------------|--|
| 305                     |    | Free material | Powder<br>MS·APCI (m/z) :<br>394 (M+H) +     |
| 306                     |   | Free material | Powder<br>MS·APCI (m/z) :<br>394/396 (M+H) + |
| 307                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>360/362 (M+H) + |
| 308                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>374 (M+H) +     |

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Table 21 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                  |
|-------------------------|--------------------|---------------|--|
| 309                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>356 (M+H) + |
| 310                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>368 (M+H) + |
| 311                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>379 (M+H) + |
| 312                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>366 (M+H) + |

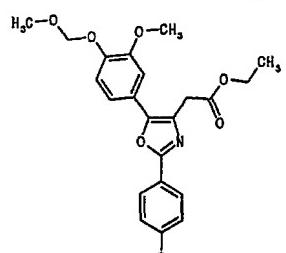
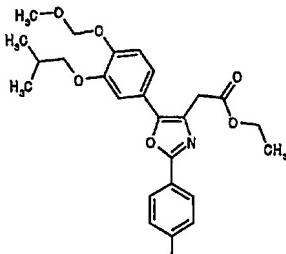
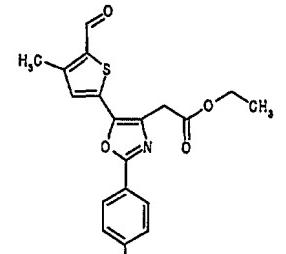
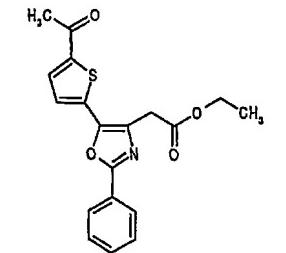
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Table 21 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                  |
|-------------------------|--------------------|---------------|--|
| 313                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>374 (M+H) + |
| 314                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>418 (M+H) + |
| 315                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>378 (M+H) + |
| 316                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>362 (M+H) + |

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Table 21 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.               |
|-------------------------|---|---------------|---------------------------------------|
| 317                     |    | Free material | Powder<br>MS·APCI (m/z) : 416 (M+H) + |
| 318                     |   | Free material | Powder<br>MS·APCI (m/z) : 468 (M+H) + |
| 319                     |  | Free material | Powder<br>MS·APCI (m/z) : 374 (M+H) + |
| 320                     |  | Free material | Powder<br>MS·APCI (m/z) : 374 (M+H) + |

## Preparation example 321

To a suspension of ethyl 2-(4-fluorophenyl)5-(2-thienyl)-oxazol-4-yl acetate (166 mg) in chloroform (1.5 ml) and acetic acid (1.5 ml) was added N-bromosuccinimide (94 mg), and the mixture was stirred at room temperature overnight. To the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the organic layer was collected. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was crystallized from diethyl ether-n-hexane to obtain ethyl 2-(4-fluorophenyl)-5-(5-bromothiophen-2-yl)oxazol-4-yl acetate (147 mg).

MS·APCI (m/z) : 410/412 (M<sup>+</sup>)

15

## Preparation example 322

The following compound shown in Table 22 was prepared in a manner similar to Preparation example 321 by using corresponding starting materials.

Table 22

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                             |
|-------------------------|--------------------|---------------|---|
| 322                     |                    | Free material | Powder<br>MS·APCI(m/z) : 380/382 (M+H) <sup>+</sup> |

25 Preparation example 323

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A mixed solution of ethyl 2-(4-fluorophenyl)-5-[3-(2-methylpropoxy)-4-methoxymethoxyphenyl]oxazol-4-yl acetate (300 mg), 4N hydrogen chloride-dioxane solution (5 ml) and ethanol (5 ml) was stirred at room temperature overnight. After 5 the solvent was removed under reduced pressure, the residue was triturated with diethyl ether and washed with n-hexane to obtain ethyl 2-(4-fluorophenyl)-5-[3-(2-methylpropoxy)-4-hydroxyphenyl]oxazol-4-yl acetate (269 mg).

MS·APCI (m/z) : 414 (MH<sup>+</sup>)

10

#### Preparation example 324

The following compound shown in Table 23 was prepared in a manner similar to Preparation example 323 by using corresponding 15 starting materials.

Table 23

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                         |
|-------------------------|--------------------|---------------|---|
| 324                     |                    | Free material | Powder<br>MS·APCI(m/z) : 372 (M+H) <sup>+</sup> |

20 Preparation example 325

To a mixed solution of ethyl 2-(4-fluorophenyl)-5-(5-formyl-4-methylthiophen-2-yl)oxazol-4-yl acetate (175 mg) in ethanol (5 ml) and tetrahydrofuran (5 ml) was added sodium borohydride (54 mg), and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture were added

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water and ethyl acetate, the organic layer was collected, washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography

5 (solvent: hexane : ethyl acetate=2:1) to obtain ethyl 2-(4-fluorophenyl)-5-(5-hydroxymethyl-4-methylthiophen-2-yl)oxazol-4-yl acetate (125 mg) as pale yellowish powder.  
MS·APCI (m/z): 376 (MH<sup>+</sup>)

10 Preparation example 326

The following compound shown in Table 24 was prepared in a manner similar to Preparation example 325 by using corresponding starting materials.

15

Table 24

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                        |
|-------------------------|--------------------|---------------|--|
| 326                     |                    | Free material | Powder<br>MS·APCI(m/z): 376 (M+H) <sup>+</sup> |

Preparation example 327

20

To a solution of ethyl 5-(3-benzyloxyphenyl)-2-(4-fluoro-phenyl)oxazol-4-yl acetate (349 mg) in methanol (20 ml) was added 10% palladium-carbon (350 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 2 hours. After the 25 reaction, palladium-carbon was removed by filtration, the residue was washed with methanol and the filtrate was

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concentrated under reduced pressure. The resulting residue was crystallized from diisopropyl ether to obtain ethyl 2-(4-fluorophenyl)-5-(3-hydroxyphenyl)oxazol-4-yl acetate (195 mg) as colorless crystal.

- 5 Melting point: 175 to 177°C  
MS·APCI (m/z): 342 (MH<sup>+</sup>)

Preparation example 328

- 10 To a solution of ethyl 2-[2-(4-fluorophenyl)-5-(3-thienyl)-oxazol-4-yl]-2-methylpropionate (54 mg) in methylene chloride (3 ml) was added boron tribromide (0.45 ml, 1.0M methylene chloride solution) under ice-cooling, and the mixture was allowed to warm to room temperature. To the mixture, another portion  
15 of boron tribromide (1.05 ml, 1.0M methylene chloride solution) was added to the mixture, and the resulting mixture was stirred at room temperature for 18 hours. To the reaction mixture were added water and ethyl acetate, the organic layer was collected, washed with brine and dried over anhydrous sodium sulfate, and  
20 the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : methanol= 15:1) to obtain 2-[2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl]-2-methylpropionic acid (32 mg). The product was dissolved in methanol, sodium  
25 methoxide (0.19 ml, 0.5M methanol solution) was added to the solution and after the mixture was stirred for 10 minutes, the solvent was removed under reduced pressure. The resulting residue was triturated with acetone to obtain sodium  
30 2-[2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl]-2-methyl-propionate (30 mg) as pale brownish powder.

MS·ESI (m/z): 330 (M-Na)

Preparation example 329

- 35 To a solution of ethyl 2-(4-fluorophenyl)-5-(3-thienyl)-oxazol-4-yl acetate (130 mg) in N,N-dimethylformamide (5 ml)

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was added sodium hydride (47 mg, 60% mineral oil) under ice-cooling, and the mixture was stirred at room temperature under argon atmosphere for 20 minutes. To the mixture was added methyl iodide (0.06 ml) in an ice bath, and the resulting mixture  
5 was stirred at room temperature for 14 hours. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate, the organic layer was collected. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure.  
10 The resulting residue was purified by silica gel column chromatography (solvent: n-hexane : diisopropyl ether=5:1) to obtain ethyl 2-[2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl]-2-methylpropionate (62 mg) as colorless oil.  
MS·APCI (m/z): 360 (MH+)

15

Preparation example 330

A solution of ethyl 2-(6-chloropyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (150 mg) in 50% aqueous  
20 dimethylamine solution (656 mg) and ethanol (3 ml) was refluxed for 16 hours. After cooling, water and ethyl acetate were added to the reaction mixture, and the organic layer was collected, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by  
25 silica gel column chromatography (solvent: chloroform : ethyl acetate=7:1) to obtain ethyl 2-(6-dimethylaminopyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (54 mg) as pale yellowish solid.

30

Preparation examples 331 and 332

The following compounds shown in Table 25 were prepared in a manner similar to Preparation example 330 by using corresponding  
35 starting materials.

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Table 25

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                 |
|-------------------------|--------------------|---------------|---|
| 331                     |                    | Free material | Powder<br>MS·APCI(m/z) :<br>358 (M+H) + |
| 332                     |                    | Free material | Powder<br>MS·APCI(m/z) :<br>358 (M+H) + |

## Preparation example 333

5

A mixture of methyl 3-(5-benzo[b]furoylamino)-4-(3-thienyl)-4-oxobutyrate (240 mg) and phosphorus oxychloride (0.19 ml) in N,N-dimethylformamide (4.8 ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into water, neutralized by a saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=20:1) to obtain methyl 2-(5-benzo[b]furyl)-5-(3-thienyl)oxazole-4-yl acetate (121 mg) as colorless powder.

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MS·APCI (m/z): 340 (MH<sup>+</sup>)

Preparation examples 334 to 336

- 5 The following compounds shown in Table 26 were prepared in a manner similar to one of the above-mentioned Preparation examples, or conventionally known preparation processes as described in U.S. Patent No. 3,470,195 and the like.

10

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Table 26

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                  |
|-------------------------|--------------------|---------------|--|
| 334                     |                    | Free material |  |
| 335                     |                    | Free material |  |
| 336                     |                    | Free material | Powder<br>MS·APCI (m/z) :<br>250 (M+H) + |

## Preparation example 337

5

To a solution of 2-[(4-fluorobenzoylamino)acetyl]thiophene (527 mg) in N,N-dimethylformamide (10 ml) was added sodium hydride (88 mg, 60% mineral oil) under ice-cooling, and the mixture was stirred under argon atmosphere at room temperature 10 for one hour. After ice-cooling, acrylonitrile (127 ml) was

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added to the mixture and the mixture was stirred at room temperature for 3 hours. After addition of ice-water, the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was dissolved in N,N-dimethylformamide (10 ml), and phosphoryl chloride (240  $\mu$ l) was added to the solution under ice-cooling. The mixture was stirred under argon atmosphere at room temperature for 3 hours. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, the mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate= 9:1→7:1), and triturated with hexane and ethyl acetate to obtain 4-(2-cyanoethyl)-2-(4-fluorophenyl)-5-(2-thienyl)oxazole (132 mg) as colorless powder.

MS·APCI (m/z): 299 (MH<sup>+</sup>)

20 Preparation example 338

A mixture of 4-(2-cyanoethyl)-2-(4-fluorophenyl)-5-(2-thienyl)oxazole (95 mg), conc. hydrochloric acid (3 ml) and formic acid (4 ml) was stirred at 60°C overnight. After addition of conc. hydrochloric acid (1 ml), the mixture was stirred at 70°C for 6 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform:methanol=19:1). The resulting colorless powder was dissolved in methanol (5 ml), 0.5M sodium methoxide (600  $\mu$ l, methanol solution) was added to the solution and the solvent was removed under reduced pressure. The resulting residue was triturated with acetone to obtain 2-(4-fluorophenyl)-5-(2-thienyl)oxazole-4-yl propionic acid

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sodium salt (103 mg) as pale brownish powder.

MS·ESI (m/z): 316 (M-Na)

Preparation example 339

5

(1) To a suspension of tellurium powder (153 mg) in ethanol (3 ml) was added sodium borohydride (108 mg), and the mixture was refluxed under argon atmosphere for 15 minutes. Under ice-cooling, acetic acid (160 µl) and a solution of ethyl

10 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazole-4-yl acrylate (302 mg) in tetrahydrofuran (4 ml) were added to the mixture, and the resulting mixture was stirred at room temperature for one hour. The reaction mixture was filtered through Cellite and the residue was washed with ethyl acetate.

15 The filtrate was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=30:1), and triturated with hexane to obtain a crude product of ethyl  
20 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazole-4-yl propionate (263 mg) as colorless powder.

(2) To a solution of the product obtained in the above-mentioned (1) (63 mg) in tetrahydrofuran (1 ml) and ethanol (2 ml) was added 1N aqueous sodium hydroxide solution (170 µl) and the resulting mixture was refluxed for 1.5 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The resulting residue was triturated with acetone to obtain 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazole-4-yl  
30 propionic acid sodium salt (60 mg) as colorless powder.

MS·ESI (m/z): 350/352 (M-Na)

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Preparation example 340

(1) A mixture of 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)-4-hydroxymethyloxazole (1.44 g) and manganese dioxide (4.76 g) in tetrahydrofuran (20 ml) was refluxed for 3 hours. The reaction mixture was filtered through Cellite and the filtrate was concentrated under reduced pressure. The resulting residue was triturated with diethyl ether to obtain 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)-4-formyloxazole (943 mg) as colorless powder.

MS·APCI (m/z) : 308 (MH<sup>+</sup>)

(2) To a solution of ethyl diethylphosphonoacetate (740 µl) in tetrahydrofuran (12 ml) was added sodium hydride (153 mg, 60% mineral oil) in an ice-acetone bath, and the resulting mixture was stirred at the same temperature for 15 minutes. 5-(5-Chlorothiophen-2-yl)-2-(4-fluorophenyl)-4-formyloxazole (400 mg) was added to the mixture and the mixture was allowed to warm to room temperature for one hour. After cooling, the reaction mixture was neutralized by a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=30:1), and then, triturated with diethyl ether and hexane to obtain 404 mg of ethyl 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazole-4-yl acrylate as colorless powder.

MS·APCI (m/z) : 378 (MH<sup>+</sup>)

30

Preparation example 341

A mixture of 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)-4-methoxycarbonyloxazole (1.8 g) and lithium borohydride (580 mg) in tetrahydrofuran (40 ml) was stirred at room temperature for one hour, and then, refluxed for 1.5 hours. After cooling, water

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and 10% hydrochloric acid were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The 5 resulting residue was triturated with diethyl ether-ethyl acetate to obtain 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)-4-hydroxymethyloxazole (1.48 g) as colorless powder.  
MS·APCI (m/z): 310/312 (MH+)

10 Preparation example 342

In a manner similar to Preparation example 341 by using the corresponding starting materials, 5-(4-chloro-3-fluorophenyl)-2-(4-fluorophenyl)-4-hydroxymethyloxazole was 15 obtained.

MS·APCI (m/z): 322/324 (MH+)

Preparation example 343

20 To a solution of ethyl 2-(4-fluorophenyl)oxazole-4-carboxylate (7.44 g) in chloroform (100 ml) was added dropwise bromine (8.1 ml) at room temperature, and the resulting mixture was stirred at room temperature for 30 minutes and then refluxed for 8 hours. After cooling the reaction mixture, 10% aqueous sodium 25 thiosulfate solution was added to the mixture and the mixture was extracted with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by 30 silica gel column chromatography (solvent: ethyl acetate : n-hexane=1:9) to obtain ethyl 5-bromo-2-(4-fluorophenyl)-oxazol-4-carboxylate (9.21 g) as pale yellowish powder.

MS·APCI (m/z): 314/316 (MH+)

35 Preparation example 344

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To a solution of methyl 3-(5-chlorothiophen-2-yl)-2-(4-fluorobenzoylamino)-3-oxopropionate (7.25 g) in N,N-dimethyl-formamide (80 ml) was added dropwise phosphorus oxychloride (5.7 ml) under ice-cooling, and the mixture was then stirred at room 5 temperature for 3 days. After cooling, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica 10 gel column chromatography (solvent: hexane : ethyl acetate= 100:1), and then, triturated with diethyl ether-hexane to obtain methyl 5-(5-chloro-thiophen-2-yl)-2-(4-fluorophenyl)oxazol-4-carboxylate (2.8 g) as colorless powder.

MS·APCI (m/z): 338/340 (MH<sup>+</sup>)

15

Preparation example 345

In a manner similar to Preparation example 344 by using the corresponding starting materials, methyl 5-(3-thienyl)-2-(4-fluorophenyl)oxazol-4-carboxylate was obtained.

Preparation example 346

A mixture of ethyl 5-bromo-2-(4-fluorophenyl)oxazol-4-carboxylate (600 mg), 0.05M (4-chloro-3-fluorophenyl) zinc bromide (6 ml, tetrahydrofuran solution), and tetrakis-(triphenylphosphine) palladium (231 mg) in tetrahydrofuran (5 ml) was stirred under argon atmosphere at room temperature for 2 hours, followed by refluxing for 40 minutes. The reaction 25 mixture was cooled and concentrated under reduced pressure, and water was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was successively washed with 10% hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate 30 and the solvent was removed under reduced pressure. The residue 35 was purified by silica gel column chromatography (solvent: ethyl

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acetate : n-hexane=1:8) to obtain ethyl 5-(4-chloro-3-fluoro-phenyl)-2-(4-fluorophenyl)oxazol-4-carboxylate (580 mg) as pale reddish solid.

MS·APCI (m/z) : 364/366 (MH+)

5

Preparation example 347

A mixture of p-fluorobenzamide (5 g), ethyl bromopyruvate (9.92 ml), and sodium hydrogen carbonate (15 g) in tetrahydrofuran (150 ml) was refluxed for 20 hours. After cooling the reaction mixture, insoluble material was removed by filtration through Cellite and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 ml) and trifluoroacetic anhydride (30 ml) was added to the mixture in an ice bath. After stirring at room temperature for one hour, a saturated aqueous sodium hydrogen carbonate solution was added to the mixture in an ice bath, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: ethyl acetate : n-hexane=1:9) to obtain ethyl 2-(4-fluorophenyl)oxazol-4-carboxylate (7.44 g) as colorless solid.

MS·APCI (m/z) : 236 (MH+)

25

Preparation example 348

(1) Chlorine gas was bubbled through a suspension of 2-[5-(4-chloro-3-fluorophenyl)-2-(4-fluorophenyl)oxazol-4-yl]methylthiourea (200 mg) in water (15 ml) under ice-cooling for 5 minutes. The mixture was stirred at the same temperature for 30 minutes followed by stirring at room temperature for 30 minutes. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain a crude

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product of 5-(4-chloro-3-fluorophenyl)-2-(4-fluorophenyl)-oxazol-4-yl methanesulfonyl chloride.

(2) The product obtained in (1) was dissolved in tetrahydrofuran  
5 (3 ml), 28% aqueous ammonia (2 ml) was added to the solution,  
and the mixture was stirred at room temperature for 3 hours.  
The reaction mixture was concentrated under reduced pressure  
and the residue was purified by silica gel column chromatography  
10 (solvent: chloroform : methanol= 20:1) to obtain 5-(4-chloro-  
3-fluorophenyl)-2-(4-fluorophenyl)oxazol-4-ylmethanesulfon-  
amide (164 mg) as pale yellowish solid.

MS·APCI (m/z): 385/387 (MH<sup>+</sup>)

(3) To a solution of 5-(4-chloro-3-fluorophenyl)-2-(4-fluoro-  
15 phenyl)oxazol-4-ylmethanesulfonamide obtained in (2) (125 mg)  
in methanol was added 0.5M sodium methoxide (0.64 ml, methanol  
solution). The solvent was removed under reduced pressure, and  
the resulting residue was triturated with acetone to obtain  
5-(4-chloro-3-fluorophenyl)-2-(4-fluorophenyl)oxazol-4-yl  
20 methanesulfonamide sodium salt (80 mg).

MS·APCI (m/z): 383/385 (MH<sup>+</sup>)

#### Preparation example 349

25 (1) A solution of 5-(4-chloro-3-fluorophenyl)-2-(4-fluoro-  
phenyl)-4-hydroxymethyloxazole (965 mg) and thionyl chloride  
(1.1 ml) in tetrahydrofuran (30 ml) was stirred at 0°C for 30  
minutes, followed by stirring at room temperature for 2 hours.  
Additional thionyl chloride (1.1 ml) was added to the mixture  
30 and the mixture was refluxed for one hour. The reaction mixture  
was concentrated under reduced pressure. The remaining  
volatiles were removed by evaporation with toluene, and further  
dried under reduced pressure to obtain a crude product of  
5-(4-chloro-3-fluorophenyl)-4-chloromethyl-2-(4-fluoro-  
35 phenyl)oxazole (925 mg).

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(2) A solution of the crude product obtained in (1) (925 mg) and thiourea (269 mg) in tetrahydrofuran (50 ml) was refluxed for 15 hours. The reaction mixture was concentrated under reduced pressure to one-third volume, and the residue was  
5 triturated with adding diethyl ether to obtain 2-[5-(4-chloro-3-fluorophenyl)-2-(4-fluorophenyl)-oxazol-4-yl]-methylthiourea hydrochloride (954 mg).

MS·APCI (m/z) : 380/382 (MH<sup>+</sup>)

10 Preparation example 350

To a solution of 5-(2-cyanoethyl)-2-(4-fluorophenyl)-4-(2-methoxyphenyl)imidazole (40 mg) in dichloromethane (10 ml) was added dropwise boron tribromide (94 mg) under ice-cooling, and  
15 the mixture was stirred at room temperature overnight. To the reaction mixture was added dropwise a saturated aqueous sodium hydrogen carbonate solution under ice-cooling, and then, the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed  
20 under reduced pressure. The residue was purified by preparative TLC (solvent: hexane : ethyl acetate=1:1), and further purified by NH silica gel column chromatography (solvent: hexane : ethyl acetate=1:1). To the product was added hydrogen chloride-ethanol solution and the mixture was concentrated to obtain  
25 5-(2-cyanoethyl)-2-(4-fluorophenyl)-4-(2-hydroxyphenyl)-imidazole hydrochloride (6 mg) as colorless solid.

MS·APCI (m/z) : 308 (MH<sup>+</sup>)

Preparation examples 351 to 355

30

The following compounds shown in Table 27 were prepared in a manner similar to Preparation examples 43 and Preparation example 152 by using the corresponding starting materials.

35

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Table 27

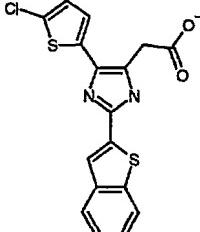
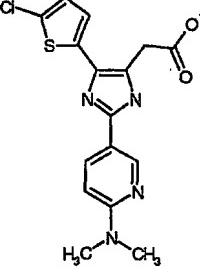
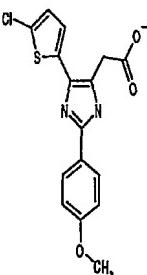
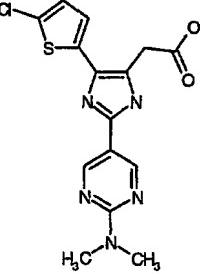
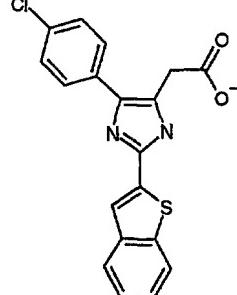
| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 351                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>373/375 (M-Na) - |
| 352                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>361/363 (M-H)    |
| 353                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>347/349 (M-Na)   |
| 354                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>362/364 (M-Na)   |

Table 27 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                   |
|-------------------------|---|------|---|
| 355                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>367/369 (M-H) |

## Preparation example 356

5

A mixture of ethyl 2-(6-aminopyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (70 mg) and 40% aqueous chloroacetoaldehyde solution (47  $\mu$ l) in ethanol (2.1 ml) was refluxed for 3 hours, and 40% aqueous chloroacetoaldehyde

10 solution (16  $\mu$ l) was added to the mixture and the resulting mixture was refluxed for one hour. After cooling, a saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, the mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent was removed under 15 reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : methanol= 49:1 → 97:3) to obtain ethyl 2-(imidazo[1,2-a]pyridin-5-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (65 mg).

MS·APCI (m/z) : 388/390 (MH $^+$ )

20

## Preparation example 357

(1) To a solution of ethyl 2-(6-chloropyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (1 g) in N,N-di-25 methylformaldehyde (10 ml) was added sodium azide (1.7 g), and the mixture was refluxed overnight. After cooling, water was added to the reaction mixture and the mixture was extracted with

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ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : ethyl acetate=8:1) to obtain ethyl 2-(6-azidopyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (401 mg) as yellowish powder.

(2) A mixture of ethyl 2-(6-azidopyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (401 mg) and 540 mg of triphenylphosphine (540 mg) in water (2 ml) and acetic acid (8 ml) was refluxed for 2 hours. After cooling, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : ethyl acetate=5:1→2:3→1:2), and then, triturated with diethyl ether to obtain ethyl 2-(6-aminopyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (177 mg) as yellowish powder.

MS·APCI (m/z): 364/366 (MH+)

#### Preparation example 358

A mixture of ethyl 5-(5-chlorothiophen-2-yl)-2-(1-formyl-indolin-5-yl)oxazol-4-yl acetate (160 mg) and 6N hydrochloric acid (2 ml) in ethanol (4 ml) was stirred at 60°C for 4 days. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (solvent: chloroform : methanol=20:1) to obtain ethyl 5-(5-chlorothiophen-2-yl)-2-(5-indolinyl)oxazol-4-yl acetate (53 mg) as colorless powder.

MS·APCI (m/z): 389/391 (MH+)

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Preparation example 359

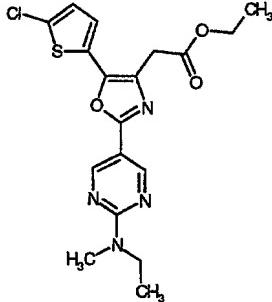
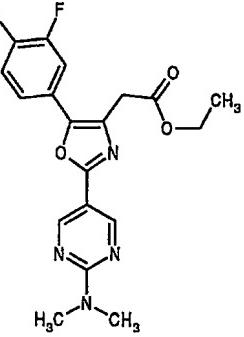
To a suspension of ethyl 2-(2-methylthiopyrimidin-5-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (156 mg) in  
5 tetrahydrofuran (3.12 ml) was added metachloroperbenzoic acid  
(88 mg, 70% purity) under ice-cooling, and the mixture was stirred  
at room temperature for one hour. After ice-cooling again, 70%  
metachloroperbenzoic acid (40 mg) was added to the mixture and  
the resulting mixture was stirred at room temperature for one  
10 hour. To the mixture was added 50% aqueous dimethylamine  
solution (1 ml) and the mixture was stirred at room temperature  
for 30 minutes. Water was added to the reaction mixture and  
the mixture was extracted with chloroform. The organic layer  
was washed with brine, dried over anhydrous sodium sulfate and  
15 the solvent was removed under reduced pressure. The resulting  
residue was purified by silica gel column chromatography  
(solvent: chloroform : ethyl acetate=8:1) to obtain ethyl  
2-(2-dimethylaminopyrimidin-5-yl)-5-(5-chlorothiophen-2-yl)  
oxazol-4-yl acetate (139 mg) as colorless powder.  
20 MS·APCI (m/z): 393/395 (MH+)

Preparation examples 360 and 361

The following compounds shown in Table 28 were prepared in a  
25 manner similar to Preparation examples 359 by using the  
corresponding starting materials.

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Table 28

| Preparation example No. | Chemical structure   | Salt          | Physical constant, etc.                      |
|-------------------------|--|---------------|--|
| 360                     |   | Free material | Powder<br>MS·APCI (m/z) :<br>407/409 (M+H) + |
| 361                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>405/407 (M+H) + |

## Preparation examples 362 to 364

5

The compounds obtained in Preparation examples 359 to 361 were subjected to hydrolysis according to the conventional manner to obtain the compounds shown in Table 29.

10

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Table 29

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 362                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>363/365 (M-Na) - |
| 363                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>377/379 (M-Na) - |
| 364                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>375/377 (M-Na) - |

## Preparation example 365

5

To a suspension of ethyl 2-(6-chloropyridin-3-yl)-5-(3-thienyl)oxazol-4-yl acetate (150 mg) in ethanol (3 ml) was added 15% aqueous sodium methyl sulfide solution (2 ml), and the mixture was refluxed for 3 days. After cooling, the reaction mixture

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was neutralized by 10% hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was washed with diethyl ether and dissolved  
5 in methanol (5 ml), and 0.5M sodium methoxide (495  $\mu$ l, methanol solution) was added to the solution and the solvent was removed under reduced pressure. The resulting residue was triturated with acetone to obtain 2-(6-methylthiopyridin-3-yl)-5-(3-thienyl)oxazol-4-yl acetic acid sodium salt (74 mg) as pale  
10 yellowish powder.

MS·ESI (m/z): 331 (M-Na)

Preparation example 366

15 In a manner similar to Preparation example 365 and using corresponding starting materials, 2-(6-methylthiopyridin-3-yl)-5-(2-thienyl)oxazol-4-yl acetic acid sodium salt was obtained.

MS·ESI (m/z): 331 (M-Na)

20

Preparation example 367

To a suspension of ethyl 2-(6-chloropyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate (192 mg) in ethanol (5 ml) was added sodium hydride (100 mg, 60% mineral oil), and the mixture was refluxed for 6 hours, and then, water (1 ml) was added to the mixture and the mixture was further refluxed for 30 minutes. After cooling, the reaction mixture was neutralized by 10% hydrochloric acid, and extracted with ethyl acetate. The  
25 organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was washed with hexane and dissolved in methanol (5 ml), and 0.5M sodium methoxide (867  $\mu$ l, methanol solution) was added to the solution and the solvent was removed under reduced pressure.  
30 The resulting residue was triturated with acetone to obtain 2-(6-ethoxypyridin-3-yl)-5-(5-chlorothiophen-2-yl)oxazol-  
35

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4-yl acetic acid sodium salt (169 mg) as pale yellowish powder.  
MS·ESI (m/z): 363/365 (M-Na)

Preparation examples 368 and 369

5

The following compounds shown in Table 30 were prepared in a manner similar to Preparation examples 367 by using the corresponding starting materials.

10

Table 30

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                  |
|-------------------------|--------------------|------|--|
| 368                     |                    | Na   | Powder<br>ESI·MS (m/z): 349/351 (M-Na) - |
| 369                     |                    | Na   | Powder<br>ESI·MS (m/z): 315 (M-Na) -     |

Preparation example 370

- 15 To a mixture of 2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl acetic acid (130 mg) in N,N-dimethylformamide (5 ml) was added N,N-carbonyldiimidazole (347 mg), and the mixture was stirred at room temperature for 2 hours. Methanesulfonamide (204 mg)

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- and 1,8-diazabicyclo[5.4.0]undecene (0.32 ml) were added to the mixture and the resulting mixture was stirred at 100°C overnight. The reaction mixture was poured into 10% hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with  
 5 water and brine, and dried over anhydrous sodium sulfate, and the solvent was removed under the reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=1:1), and then, the resulting product was dissolved in methanol (10 ml), and  
 10 0.5M sodium methoxide (68 µl, methanol solution) was added to the solution and the solvent was removed under reduced pressure to obtain N-[2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl acetyl]methanesulfonamide sodium salt (42 mg) as colorless powder.  
 15 MS·ESI (m/z): 379 (M-Na)

Preparation example 371

- Corresponding starting compounds are treated in a manner similar  
 20 to Preparation example 370 to obtain the compound shown in Table 31.

Table 31

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.           |
|-------------------------|--------------------|------|-----------------------------------|
| 371                     |                    | Na   | Powder<br>ESI·MS (m/z): 442 (M-H) |

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Preparation example 372

To a mixture of ethyl 2-(4-fluorophenyl)-5-(5-chlorothiophen-2-yl)oxazol-4-yl acetate(1.01 g) in ethanol (5 ml), diethyl ether (5 ml) and tetrahydrofuran (6 ml) was added sodium hydride (110 mg, 60% mineral oil) under argon atmosphere, and the mixture was stirred for 10 minutes under ice-cooling. After addition of isoamyl nitrite (647 mg), the mixture was stirred at room temperature for 1.5 hours. 10% Hydrochloric acid was added to the mixture and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting crude product (395 mg) was taken up into formic acid (4 ml) and ethanol (3 ml). To the mixture zinc powder (291 mg) was added at room temperature, and the mixture was stirred for 10 minutes followed by stirring at 70°C for 20 minutes. After cooling, the reaction mixture was filtered through glass filter, the residue was washed with ethanol and the filtrate was concentrated under reduced pressure. To the resulting residue was added a saturated aqueous sodium hydrogen carbonate solution, the mixture was extracted with ethyl acetate and the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was triturated with diethyl ether-hexane to obtain ethyl 2-amino-2-[5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)-oxazol-4-yl]acetate (307 mg) as colorless powder.

MS·APCI (m/z): 381/383 (MH<sup>+</sup>)

30 Preparation example 373

A mixture 2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl acetic acid (100 mg), methoxyamine hydrochloride (37.6 mg), 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride (95 mg), 1-hydroxybenzotriazole (67 mg) and triethylamine (0.14 ml) in N,N-dimethylformamide (3 ml) was stirred at room

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temperature overnight. Water was added to the reaction mixture, the mixture was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The 5 resulting residue was purified by silica gel column chromatography (solvent: chloroform : methanol=20:1), and triturated with diethyl ether-hexane to obtain [2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl acetyl] N-methoxyamide (75 mg) as colorless powder.

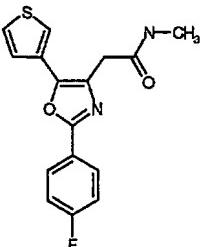
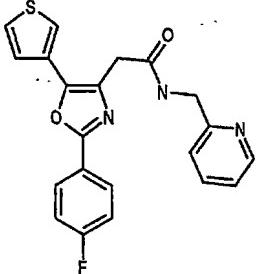
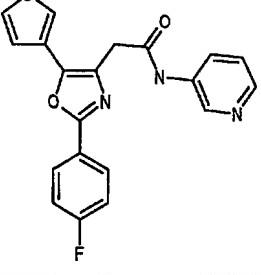
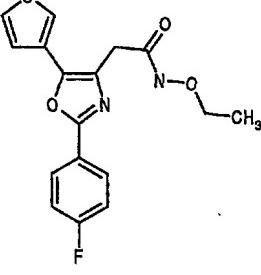
10 MS·APCI (m/z): 333 (MH+)

Preparation examples 374 to 377

The corresponding starting materials were treated in a manner 15 similar to Preparation example 373 to obtain the compounds shown in Table 32 below.

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Table 32

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.   |
|-------------------------|---|---------------|---|
| 374                     |    | Free material | Powder<br>MS·APCI (m/z) : 317 (M+H)                                 |
| 375                     |   | HCl           | Powder<br>MS·APCI (m/z) : 394 (M+H)                                 |
| 376                     |  | HCl           | Powder<br>MS·APCI (m/z) : 380 (M+H)                                 |
| 377                     |  | Free material | Crystal<br>Melting point:<br>183-184°C<br>MS·APCI (m/z) : 347 (M+H) |

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Preparation example 378

- (1) Under argon atmosphere, to a solution of 2-(4-fluorophenyl)-4-(2-hydroxyethyl)-5-(3-thienyl)oxazole (300 mg) in 5 methylene chloride (10 ml) were successively added methanesulfonyl chloride (96  $\mu$ l) and triethylamine (188  $\mu$ l) under ice-cooling, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water and extracted with methylene chloride. The organic layer was washed 10 with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain a crude product of 2-(4-fluorophenyl)-4-(2-methanesulfonyloxyethyl)-5-(3-thienyl)oxazole.
- 15 (2) To a solution of methanesulfonamide (136 mg) in N,N-dimethylformamide (10 ml) was added sodium hydride (57 mg, 60% mineral oil) under ice-cooling, and the mixture was stirred at room temperature for one hour. After the mixture was ice-cooled again, an N,N-dimethylformamide solution of the crude product 20 obtained in (1) was added to the mixture and the resulting mixture was stirred at room temperature for one hour and then stirred at 60°C overnight. The reaction mixture was ice-cooled, and then, poured into an aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with 25 water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. After the resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=4:1), the obtained product was dissolved in methanol (5 ml), and 0.5M sodium methoxide (562  $\mu$ l, 30 methanol solution) was added to the solution and the solvent was removed under reduced pressure to obtain 2-(4-fluorophenyl)-4-methanesulfonylaminoethyl-5-(3-thienyl)oxazole sodium salt (143 mg) as colorless powder.
- MS·ESI (m/z): 365 (M-Na)

## Preparation example 379

(1) A mixture of 2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl acetic acid (1.5 g), diphenylphosphoryl azide (1.28 ml) and 5 triethylamine (0.83 ml) in t-butanol (30 ml) was refluxed for one day. After cooling the reaction mixture, the solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate 10 solution and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Chloroform was added to the residue, the mixture was heated and insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified 15 by silica gel column chromatography (solvent: ethyl acetate : n-hexane=1:9→1:7) to obtain 4-(t-butoxycarbonylamino)methyl-2-(4-fluorophenyl)-5-(3-thienyl)oxazole (501 mg).

MS·APCI (m/z): 375 (MH<sup>+</sup>)

20 (2) A solution of 4-(t-butoxycarbonylamino)methyl-2-(4-fluorophenyl)-5-(3-thienyl)oxazole (455 mg) in 4N hydrogen chloride-dioxane solution was stirred at room temperature for 13 hours. The reaction mixture was concentrated under reduced pressure and the remaining volatiles were removed by evaporation 25 with toluene, and the resulting residue was triturated with diethyl ether to obtain 4-aminomethyl-2-(4-fluorophenyl)-5-(3-thienyl)oxazole hydrochloride (288 mg) as colorless powder.

MS·APCI (m/z): 275 (MH<sup>+</sup>)

## 30 Preparation example 380

(1) To a suspension of 4-aminomethyl-2-(4-fluorophenyl)-5-(3-thienyl)oxazole (110 mg) in dichloromethane (5 ml) were successively added dropwise under acetone-ice cooling 35 methanesulfonyl chloride (0.036ml) and triethylamine (0.15 ml). The reaction mixture was stirred at 0°C for one hour, and further

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stirred at room temperature for 2 hours. To the reaction mixture was added a saturated aqueous ammonium chloride solution and extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent: chloroform : methanol=100:0→95:5) to obtain a crude product of N-[2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl]-methanesulfonamide (140 mg).

10

(2) Crude N-[2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl]-methanesulfonamide (133 mg) was dissolved in methanol (5 ml) and tetrahydrofuran (5 ml), and 0.5M sodium methoxide (0.72 ml, methanol solution) was added to the solution and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with acetone to obtain N-[2-(4-fluorophenyl)-5-(3-thienyl)oxazol-4-yl]methanesulfonamide sodium salt (112 mg).

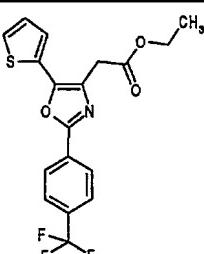
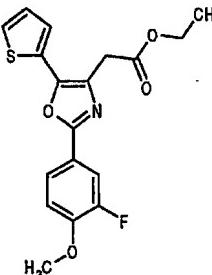
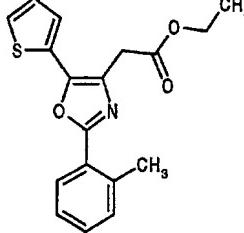
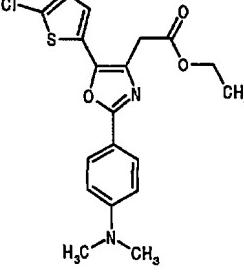
15 20 MS·APCI (m/z): 353 (MH<sup>+</sup>)

#### Preparation examples 381 to 429

The following compounds shown in Table 33 were prepared in a manner similar to Preparation example 63 by using corresponding starting materials.

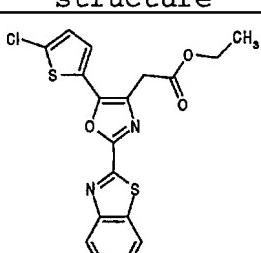
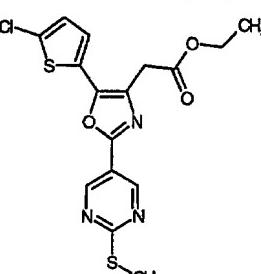
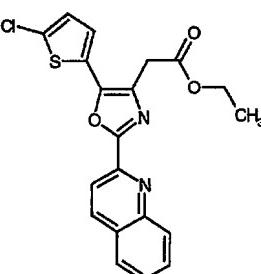
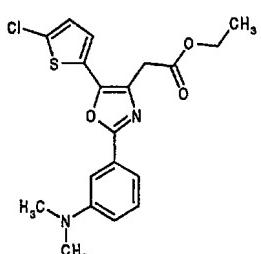
- 165 -

Table 33

| Preparation example No. | Chemical structure  | Salt          | Physical property, etc.  |
|-------------------------|---|---------------|--|
| 381                     |    | Free material | Crystal<br>Melting point:<br>108.5-109°C<br>MS·APCI (m/z) :<br>381 (M+H) |
| 382                     |   | Free material | Crystal<br>Melting point:<br>117-117.5°C<br>MS·APCI (m/z) :<br>362 (M+H) |
| 383                     |  | Free material | Crystal<br>Melting point:<br>67-68°C<br>MS·APCI (m/z) :<br>382 (M+H)     |
| 384                     |  | Free material | Crystal<br>Melting point:<br>118-119°C<br>MS·APCI (m/z) :<br>391 (M+H)   |

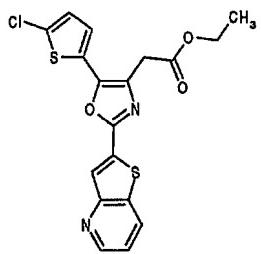
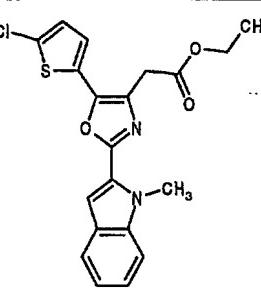
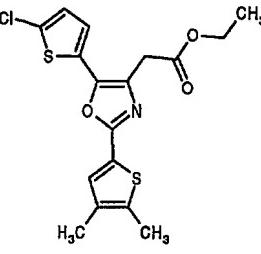
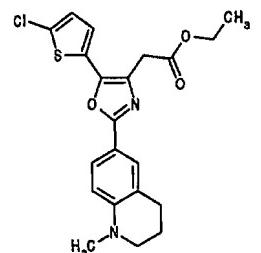
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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 385                     |    | Free material | Powder<br>MS·APCI (m/z) : 405/407 (M+H) + |
| 386                     |   | Free material | Powder<br>MS·APCI (m/z) : 396/398 (M+H) + |
| 387                     |  | Free material | Powder<br>MS·APCI (m/z) : 399/401 (M+H)   |
| 388                     |  | Free material | Powder<br>MS·APCI (m/z) : 391/393 (M+H) + |

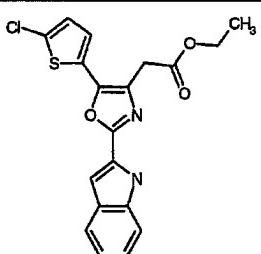
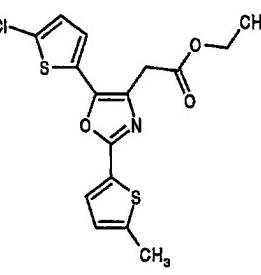
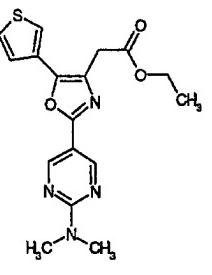
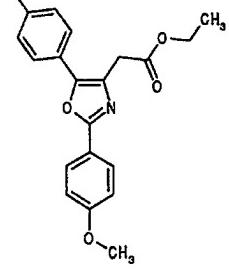
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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                     |
|-------------------------|---|---------------|---|
| 389                     |    | Free material | Powder<br>MS·APCI(m/z) :<br>405/407 (M+H) + |
| 390                     |   | Free material | Powder<br>MS·APCI(m/z) :<br>401/403 (M+H) + |
| 391                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>382/384 (M+H) + |
| 392                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>417/419 (M+H) + |

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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                     |
|-------------------------|---|---------------|---|
| 393                     |    | Free material | Powder<br>MS·APCI(m/z) :<br>387/389 (M+H) + |
| 394                     |   | Free material | Powder<br>MS·APCI(m/z) :<br>368/370 (M+H) + |
| 395                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>359 (M+H) +     |
| 396                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>372/374 (M+H) + |

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Table 33 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-------------------------|--------------------|---------------|---|
| 397                     |                    | Free material | Powder<br>MS·APCI (m/z) : 387/389 (M+H) + |
| 398                     |                    | Free material | Powder<br>MS·APCI (m/z) : 376/378 (M+H) + |
| 399                     |                    | Free material | Powder<br>MS·APCI (m/z) : 394/396 (M+H) + |
| 400                     |                    | Free material | Powder<br>MS·APCI (m/z) : 400/402 (M+H) + |

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Table 33 (contd.)

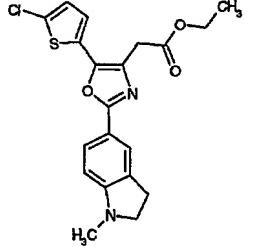
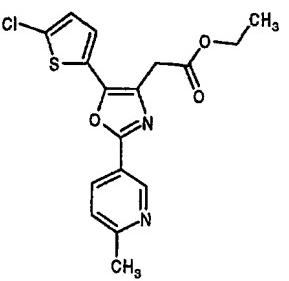
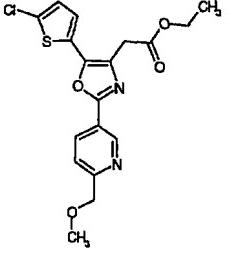
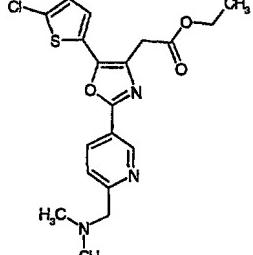
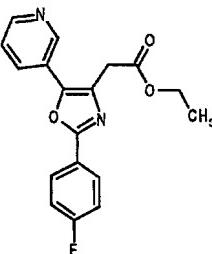
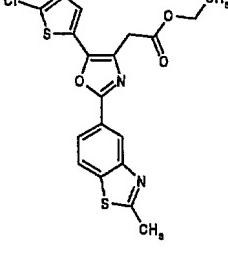
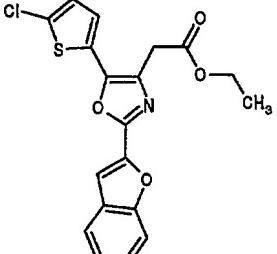
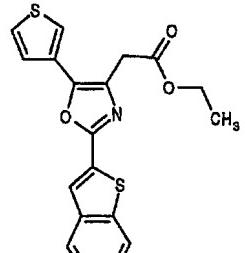
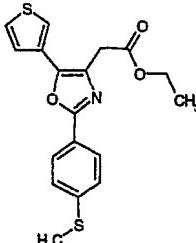
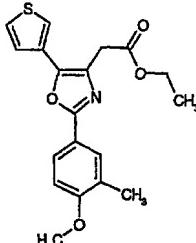
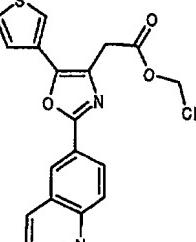
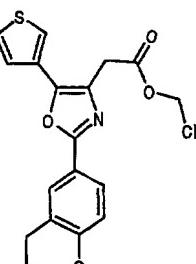
| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 401                     |    | Free material | Powder<br>MS·APCI (m/z) : 403/405 (M+H) + |
| 402                     |   | Free material | Powder<br>ESI·MS (m/z) : 333/335 (M-Na) - |
| 403                     |  | Free material | Powder<br>MS·APCI (m/z) : 393/395 (M+H) + |
| 404                     |  | Free material | Powder<br>MS·APCI (m/z) : 406/408 (M+H) + |

Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.   |
|-------------------------|---|---------------|---|
| 405                     |    | Free material | Powder<br>MS·APCI (m/z) : 327 (M+H)                                     |
| 406                     |   | Free material | Powder<br>MS·APCI (m/z) : 418/420 (M+H) +                               |
| 407                     |  | Free material | Powder<br>MS·APCI (m/z) : 388/390 (M+H)                                 |
| 408                     |  | Free material | Crystal<br>Melting point:<br>155-156.5°C<br>MS·APCI (m/z) : 370 (M+H) + |

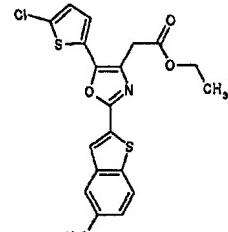
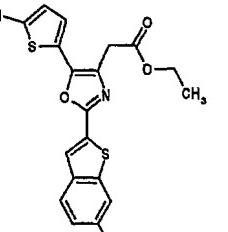
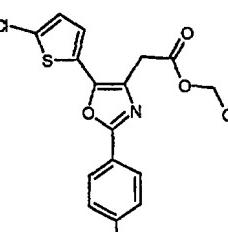
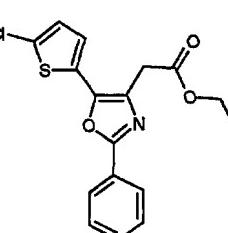
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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.  |
|-------------------------|---|---------------|--|
| 409                     |    | Free material | Crystal<br>Melting point:<br>77-78°C<br>MS·APCI (m/z) : 360<br>(M+H) + |
| 410                     |    | Free material | Crystal<br>Melting point:<br>84-86°C<br>MS·APCI (m/z) : 358 (M+H) +    |
| 411                     |  | Free material | Crystal<br>Melting point:<br>130-133°C<br>MS·APCI (m/z) : 365 (M+H) +  |
| 412                     |  | Free material | Oil<br>MS·APCI (m/z) : 370 (M+H) +                                     |

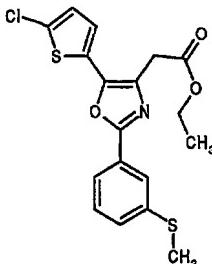
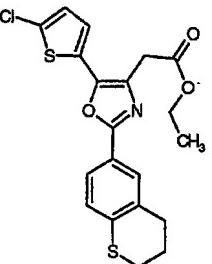
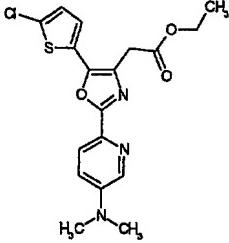
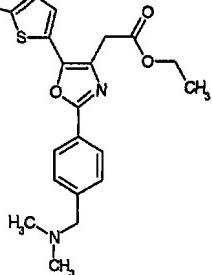
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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 413                     |    | Free material | Powder<br>MS·APCI (m/z) : 418/420 (M+H) + |
| 414                     |    | Free material | Powder<br>MS·APCI (m/z) : 422/424 (M+H) + |
| 415                     |  | Free material | Powder<br>MS·APCI (m/z) : 408/410 (M+H) + |
| 416                     |  | Free material | Powder<br>MS·APCI (m/z) : 408/410 (M+H) + |

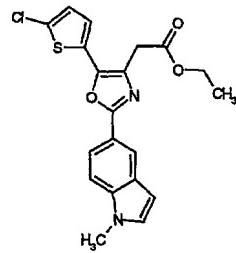
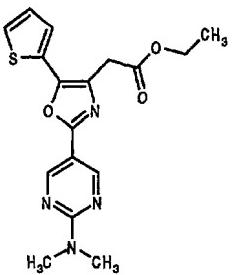
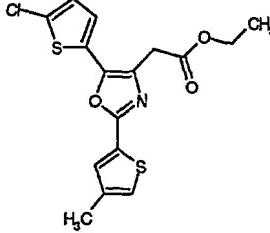
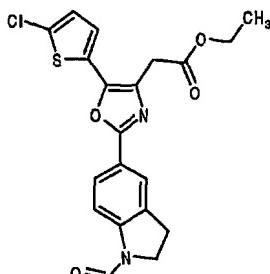
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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 417                     |    | Free material | Powder<br>MS·APCI (m/z) : 394/396 (M+H) + |
| 418                     |   | Free material | Powder<br>MS·APCI (m/z) : 420/422 (M+H) + |
| 419                     |  | Free material | Powder<br>MS·APCI (m/z) : 392/394 (M+H) + |
| 420                     |  | Free material | Powder<br>MS·APCI (m/z) : 405/407 (M+H) + |

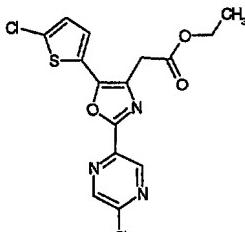
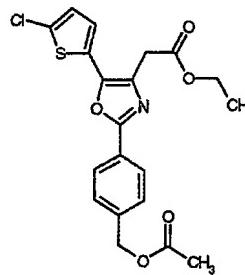
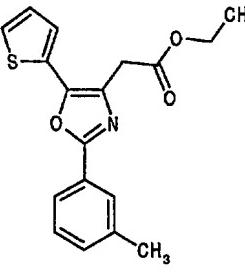
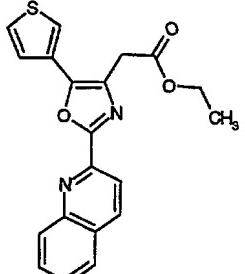
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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                     |
|-------------------------|---|---------------|---|
| 421                     |    | Free material | Powder<br>MS·APCI(m/z) :<br>401/403 (M+H) + |
| 422                     |   | Free material | Powder<br>MS·APCI(m/z) :<br>359 (M+H) +     |
| 423                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>368/370 (M+H) + |
| 424                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>417/419 (M+H) + |

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Table 33 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.  |
|-------------------------|---|---------------|--|
| 425                     |    | Free material | Powder<br>MS·APCI (m/z) : 384/386 (M+H) +                              |
| 426                     |   | Free material | Crystal<br>Melting point: 112-113°C<br>MS·APCI (m/z) : 420 (M+H) +     |
| 427                     |  | Free material | Crystal<br>Melting point: 80-81°C<br>MS·APCI (m/z) : 328 (M+H) +       |
| 428                     |  | Free material | Crystal<br>Melting point: 168.5-169.5°C<br>MS·APCI (m/z) : 365 (M+H) + |

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Table 33 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.   |
|-------------------------|--------------------|---------------|---|
| 429                     |                    | Free material | Crystal<br>Melting point:<br>145-146°C<br>MS·APCI (m/z) :<br>389/391 (M+H)+ |

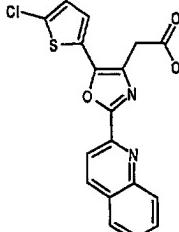
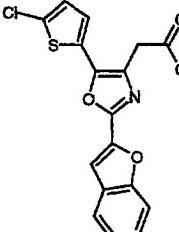
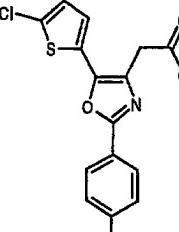
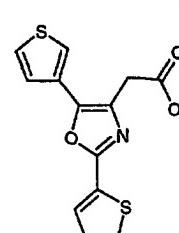
## 5 Preparation examples 430 to 479

The following compounds shown in Table 34 were prepared in a manner similar to Preparation example 148 or 152 by using corresponding starting materials.

Table 34

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Table 34 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                 |
|-------------------------|---|------|---|
| 434                     |    | Na   | Powder<br>ESI·MS (m/z) : 369 (M-Na)     |
| 435                     |    | Na   | Powder<br>ESI·MS (m/z) : 358/360 (M-Na) |
| 436                     |  | Na   | Powder<br>ESI·MS (m/z) : 348 (M-Na)     |
| 437                     |  | Na   | Powder<br>ESI·MS (m/z) : 340 (M-Na) -   |

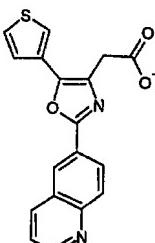
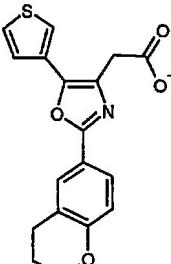
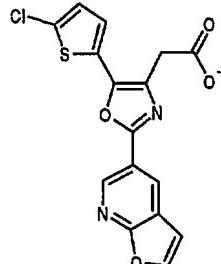
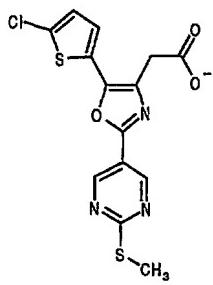
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Table 34 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                   |
|-------------------------|--------------------|------|---|
| 438                     |                    | Na   | Powder<br>ESI·MS (m/z) : 328 (M-Na) -     |
| 439                     |                    | Na   | Powder<br>ESI·MS (m/z) : 335 (M-Na) -     |
| 440                     |                    | Na   | Powder<br>ESI·MS (m/z) : 330 (M-Na) -     |
| 441                     |                    | Na   | Powder<br>ESI·MS (m/z) : 361/363 (M-Na) - |

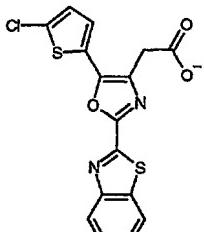
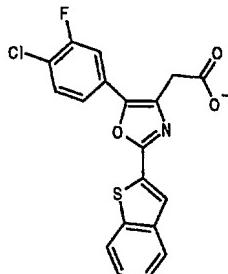
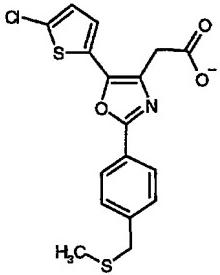
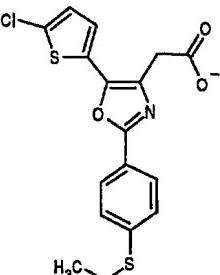
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Table 34 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                   |
|-------------------------|---|------|---|
| 442                     |    | Na   | Powder<br>ESI·MS (m/z) : 335 (M-Na) -     |
| 443                     |   | Na   | Powder<br>ESI·MS (m/z) : 340 (M-Na) -     |
| 444                     |  | Na   | Powder<br>ESI·MS (m/z) : 359/361 (M-Na) - |
| 445                     |  | Na   | Powder<br>ESI·MS (m/z) : 366/368 (M-Na) - |

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Table 34 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 446                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>375/377 (M-Na) - |
| 447                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>386/388 (M-Na) - |
| 448                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>378/380 (M-Na) - |
| 449                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>378/380 (M-Na) - |

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Table 34 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 450                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>388/390 (M-Na) - |
| 451                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>392/394 (M-Na) - |
| 452                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>333/335 (M-Na) - |
| 453                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>373/375 (M-Na) - |

Table 34 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 454                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>368/370 (M-Na) - |
| 455                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>358/360 (M-Na) - |
| 456                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>390/392 (M-Na) - |
| 457                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>364/366 (M-Na) - |

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Table 34 (contd.)

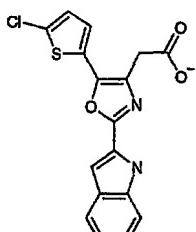
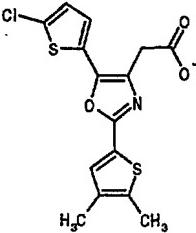
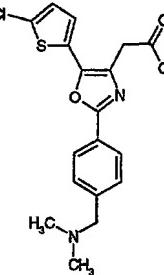
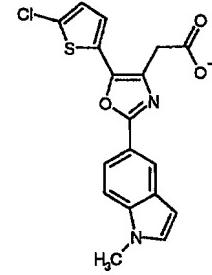
| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 458                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>338/340 (M-Na) - |
| 459                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>389/391 (M-Na) - |
| 460                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>370/372 (M-Na) - |
| 461                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>362/364 (M-Na) - |

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Table 34 (contd.)

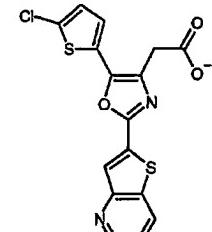
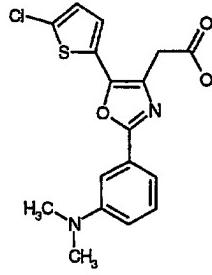
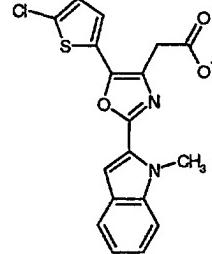
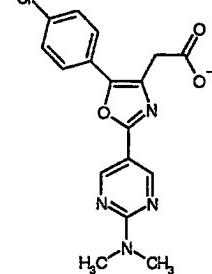
| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 462                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>378/380 (M-Na) - |
| 463                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>376/378 (M-Na) - |
| 464                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>363/365 (M-Na) - |
| 465                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>387/389 (M-Na) - |

Table 34 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 466                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>357/359 (M-Na) - |
| 467                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>352/354 (M-Na) - |
| 468                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>375/377 (M-Na) - |
| 469                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>371/373 (M-Na) - |

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Table 34 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 470                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>375/377 (M-Na) - |
| 471                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>361/363 (M-Na) - |
| 472                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>371/373 (M-Na) - |
| 473                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>357/359 (M-Na) - |

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Table 34 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                   |
|-------------------------|--------------------|------|---|
| 474                     |                    | Na   | Powder<br>ESI·MS (m/z) : 346/348 (M-Na) - |
| 475                     |                    | Na   | Powder<br>ESI·MS (m/z) : 342/344 (M-Na) - |
| 476                     |                    | Na   | Powder<br>ESI·MS (m/z) : 329 (M-Na) -     |
| 477                     |                    | Na   | Powder<br>ESI·MS (m/z) : 329 (M-Na) -     |

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Table 34 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 478                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>338/340 (M-Na) - |
| 479                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>364/366 (M-Na) - |

## 5 Preparation example 480

A mixture of ethyl 3-(4-chlorobenzoylamino)-4-phenyl-4-oxobutyrate (25 g) in acetic acid (150 ml) was heated to 130°C, and a largely excessive amount of ammonium acetate was added 10 to the mixture. After confirming completion of the reaction by TLC, the reaction mixture was cooled. Ice-water was added to the mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium 15 sulfate, and the solvent was removed under reduced pressure. The residue was crystallized from diisopropyl ether to obtain 2-(4-chlorophenyl)-4-phenylimidazol-5-yl acetamide (10.42 g). MS·EI (m/z) : 311 (M+)

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Preparation example 481

To a solution of 2-(4-chlorophenyl)-4-phenylimidazol-5-yl acetamide (10.00g) in N,N-dimethylformamide (50 ml) was added 5 dropwise 8.9 ml of phosphorus oxychloride (8.9 ml) below 20°C, and the mixture was stirred at room temperature for one hour. To the reaction mixture were added ice-water and ethyl acetate, and the mixture was neutralized by sodium hydrogen carbonate. The organic layer was collected, washed with brine, and dried 10 over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was crystallized from diisopropyl ether to obtain 2-(4-chlorophenyl)-5-cyano-methyl-4-phenylimidazole (6.85 g).

MS·EI (m/z): 293 (M+)

15

Preparation example 482

The corresponding starting materials were treated in a manner similar to Preparation example 112 to obtain 2-(5-chloro-thiophen-3-yl)-5-hydroxymethyl-4-(3-pyridyl)imidazole.

MS·APCI (m/z): 292 (MH+)

Preparation example 483

25 The corresponding starting materials were treated in a manner similar to Preparation example 130 to obtain 2-(4-fluorophenyl)-5-methylthiomethyl-4-phenylimidazole hydrochloride.

MS·APCI (m/z): 298 (M+)

30 Preparation example 484

The corresponding starting materials were treated in a manner similar to Preparation example 141 to obtain 2-(4-fluorophenyl)-5-(3-pyridyl)oxazol-4-yl acetic acid hydrochloride.

35 MS·APCI (m/z): 299 (M+)

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Preparation example 485

A mixture of 2-(2-hydroxymethylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole dihydrochloride (212 mg) and manganese oxide 5 (2 g) in tetrahydrofuran (15 ml) was refluxed for one hour. The reaction mixture was filtered and washed with tetrahydrofuran, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (solvent: chloroform : methanol=30:1→20:1) to obtain 10 2-(2-formylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole (93 mg) as orange crystal.  
MS·APCI (m/z): 284 (MH<sup>+</sup>)

Preparation example 486

15

To a solution of 2-(2-formylthiophen-3-yl)-5-ethyl-4-(3-pyridyl)imidazole (68 mg) in tetrahydrofuran (5 ml) was added dropwise 3M methyl magnesium bromide (0.24 ml, diethyl ether solution) under argon atmosphere in an ice bath, and the mixture 20 was stirred at the same temperature for 30 minutes. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced 25 pressure. The residue was purified by silica gel column chromatography (solvent: chloroform : methanol=20:1) to obtain 2-[2-(1-hydroxyethyl)thiophen-3-yl]-5-ethyl-4-(3-pyridyl)-imidazole dihydrochloride (60 mg) as orange brownish powder.  
MS·APCI (m/z): 300 (MH<sup>+</sup>)

30

Preparation example 487

(1) A mixture of ethyl 4-(2-thienyl)-2-(4-fluorophenyl)oxazol-5-yl acetate (140 mg), N-chlorosuccinic imide (62 mg) and a 35 catalytic amount of 70% aqueous perchloric acid solution in carbon tetrachloride (7 ml) was stirred at room temperature

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overnight. The reaction mixture was poured into water, neutralized by a saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=95:5) to obtain ethyl 4-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-5-yl acetate (39.6 mg) as colorless powder.

10 MS·APCI (m/z): 366/368 (MH+)

(2) The compound obtained in the above (1) was hydrolyzed according to the conventional manner to obtain 4-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-5-yl acetic acid sodium salt.

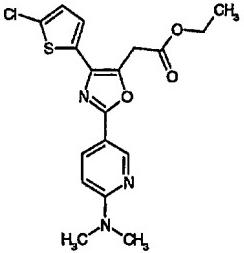
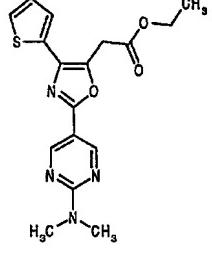
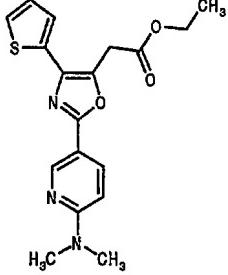
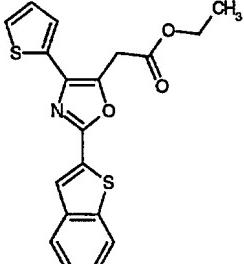
15 ESI·MS (m/z): 336/338 (M-Na)-

Preparation examples 488 to 502

20 The corresponding starting materials were treated in a manner similar to Preparation example 147 to obtain the compounds shown in Table 35 below.

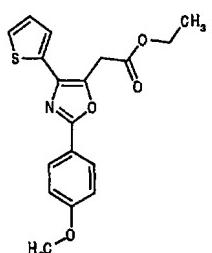
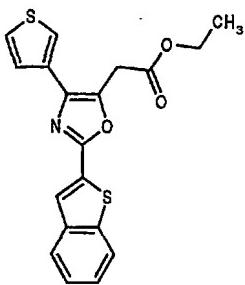
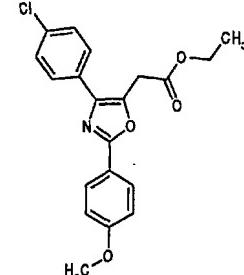
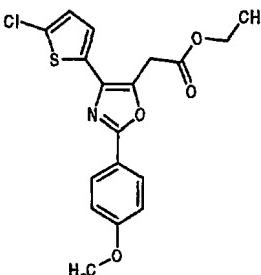
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Table 35

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                  |
|-------------------------|---|---------------|--|
| 488                     |    | Free material | Powder<br>MS·APCI(m/z) : 392/394 (M+H) + |
| 489                     |   | Free material | Powder<br>MS·APCI(m/z) : 359 (M+H) +     |
| 490                     |  | Free material | Oil<br>MS·APCI(m/z) : 358 (M+H) +        |
| 491                     |  | Free material | Powder<br>MS·APCI(m/z) : 370 (M+H) +     |

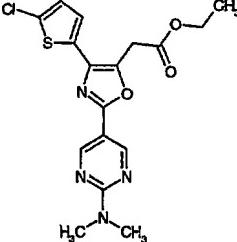
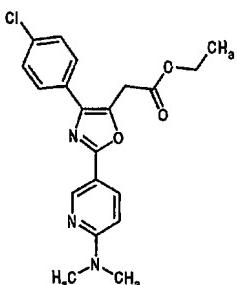
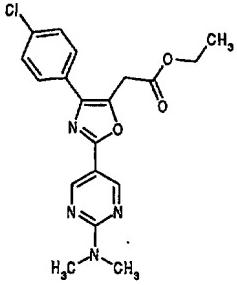
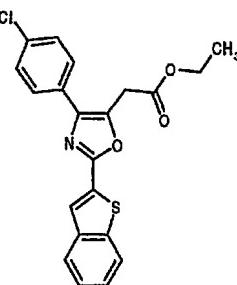
- 195 -

Table 35 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                |
|-------------------------|---|---------------|--|
| 492                     |    | Free material | Oil<br>MS·APCI (m/z) : 344 (M+H) +     |
| 493                     |   | Free material | Powder<br>MS·APCI (m/z) : 370 (M+H) +  |
| 494                     |  | Free material | Oil<br>MS·APCI (m/z) : 372/374 (M+H) + |
| 495                     |  | Free material | Oil<br>MS·APCI (m/z) : 378/380 (M+H) + |

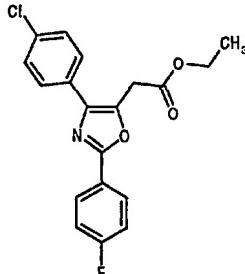
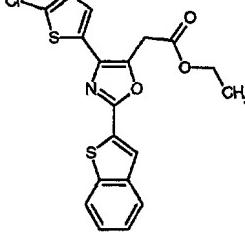
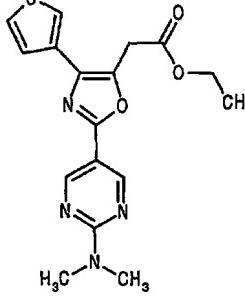
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Table 35 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                      |
|-------------------------|---|---------------|--|
| 496                     |    | Free material | Powder<br>MS·APCI (m/z) :<br>393/395 (M+H) + |
| 497                     |   | Free material | Powder<br>MS·APCI (m/z) :<br>386/388 (M+H) + |
| 498                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>387/389 (M+H) + |
| 499                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>398/400 (M+H) + |

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Table 35 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                      |
|-------------------------|---|---------------|--|
| 500                     |    | Free material | Powder<br>MS·APCI (m/z) :<br>360/362 (M+H) + |
| 501                     |   | Free material | Powder<br>MS·APCI (m/z) :<br>404/406 (M+H) + |
| 502                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>359 (M+H) +     |

## Preparation examples 503 to 517

5

The corresponding starting materials were treated in a manner similar to Preparation example 148 to obtain the compounds shown in Table 36 below.

Table 36

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 503                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>374/376 (M+Na) + |
| 504                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>362/364 (M-Na) - |
| 505                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>329 (M-Na) -     |
| 506                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>328 (M-Na) -     |

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Table 36 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                     |
|-------------------------|--------------------|------|---|
| 507                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>314 (M-Na) -    |
| 508                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>329 (M-Na) -    |
| 509                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>681 (2M-Na+H) - |
| 510                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>340 (M-H) -     |

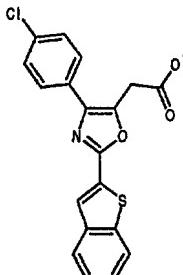
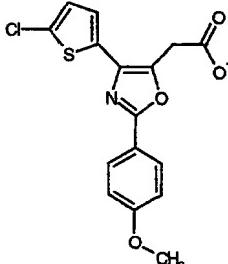
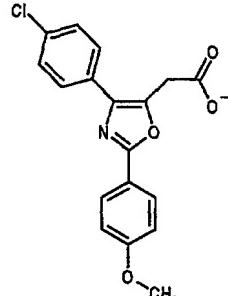
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Table 36 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 511                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>330/332 (M-Na) - |
| 512                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>363/365 (M-Na) - |
| 513                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>357/359 (M-Na) - |
| 514                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>356/358 (M-Na) - |

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Table 36 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 515                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>368/370 (M-Na) - |
| 516                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>348/350 (M-Na) - |
| 517                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>342/344 (M-Na) - |

Preparation examples 518 to 521

5

The corresponding starting materials were treated in a manner similar to Preparation example 151 or 296 to obtain the compounds shown in Table 37 below.

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Table 37

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                |
|-------------------------|--------------------|---------------|--|
| 518                     |                    | Free material | Powder<br>MS·APCI(m/z) : 351(M+H)      |
| 519                     |                    | Free material | Powder<br>MS·APCI(m/z) : 415(M+H)      |
| 520                     |                    | Free material | Powder<br>MS·APCI(m/z) : 378(M+H)      |
| 521                     |                    | Free material | Powder<br>MS·APCI(m/z) : 390/392(M+H)+ |

Preparation examples 522 to 525

5

The corresponding starting materials were treated in a manner similar to Preparation example 152 to obtain the compounds shown

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in Table 38 below.

Table 38

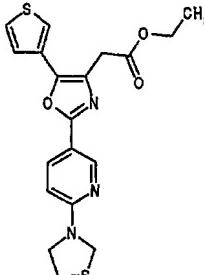
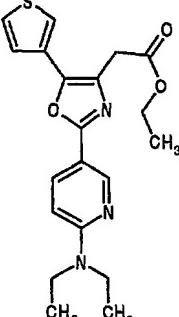
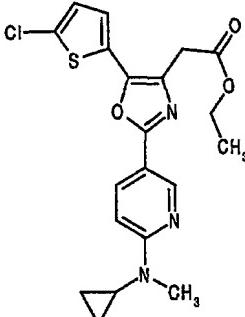
| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 522                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>321 (M-Na)       |
| 523                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>348 (M-Na)       |
| 524                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>285 (M-Na)       |
| 525                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>360/362 (M-Na) - |

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## Preparation examples 526 to 528

The corresponding starting materials were treated in a manner similar to Preparation example 330 to obtain the compounds shown  
5 in Table 39 below.

Table 39

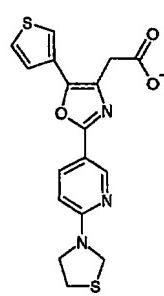
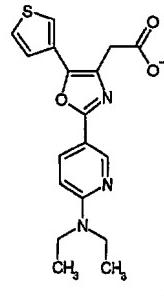
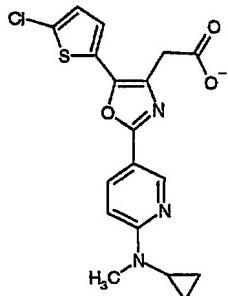
| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 526                     |    | Free material | Powder<br>MS·APCI (m/z) : 402 (M+H) +     |
| 527                     |  | Free material | Powder<br>MS·APCI (m/z) : 386 (M+H) +     |
| 528                     |  | Free material | Powder<br>MS·APCI (m/z) : 418/420 (M+H) + |

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## Preparation examples 529 to 531

The corresponding starting materials were hydrolyzed in the conventional method to obtain the compounds shown in Table 40  
5 below.

Table 40

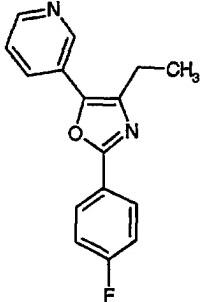
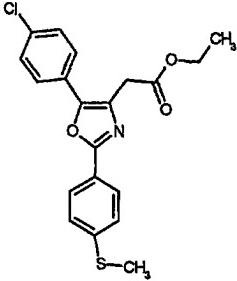
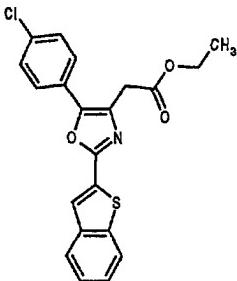
| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 529                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>372 (M-2Na+H) -  |
| 530                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>356 (M-Na) -     |
| 531                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>388/390 (M-Na) - |

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## Preparation examples 532 to 536

The corresponding starting materials were treated in a manner similar to Preparation example 227 to obtain the compounds shown 5 in Table 41 below.

Table 41

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                      |
|-------------------------|---|---------------|--|
| 532                     |   | HCl           | Powder<br>MS·APCI (m/z) :<br>269 (M+H)       |
| 533                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>388/390 (M+H) + |
| 534                     |  | Free material | Powder<br>MS·APCI (m/z) :<br>398/400 (M+H) + |

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Table 41 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-------------------------|--------------------|---------------|---|
| 535                     |                    | Free material | Powder<br>MS·APCI (m/z) : 416/418 (M+H)   |
| 536                     |                    | Free material | Powder<br>MS·APCI (m/z) : 408/410 (M+H) + |

## Preparation example 537

5

A mixture of ethyl 3-bromo-4-(5-chlorothiophen-2-yl)-4-oxo-butyrate (651 mg) and 4-fluorothiobenzamide (310 mg) in *N,N*-dimethylformamide (10 ml) was stirred at 70°C for 2 hours.

After cooling, water was added to the reaction mixture, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by NH silica gel column chromatography (solvent: hexane : ethyl acetate=10:1) to obtain ethyl 4-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)thiazol-5-yl acetate (471 mg).

MS·APCI (m/z) : 382/284 (MH+)

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Preparation examples 538 to 567

The corresponding starting materials were treated in a manner similar to Preparation example 537 to obtain the compounds shown  
5 in Table 42 below.

Table 42

| Prepara-tion example No. | Chemical structure | Salt          | Physical constant, etc.  |
|--------------------------|--------------------|---------------|--|
| 538                      |                    | Free material | Powder<br><sup>1</sup> H-NMR 300MHz (DMSO-d <sub>6</sub> ) δ 3.11(6H,s), 3.70(3H,s), 4.05(2H,s), 6.74(1H,dd), 7.52-7.58(2H,m), 7.64-7.77(2H,m), 8.00(1H,dd), 8.63-8.65(2H,m) |
| 539                      |                    | Free material | Powder<br>MS·APCI(m/z) : 374/376 (M+H)+  |
| 540                      |                    | Free material | Powder<br>MS·APCI(m/z) : 400/402 (M+H)+  |

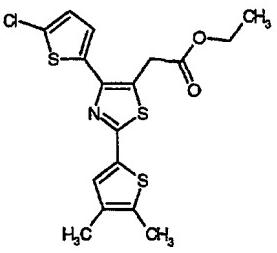
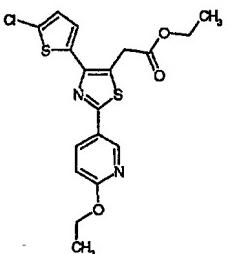
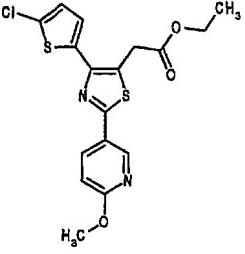
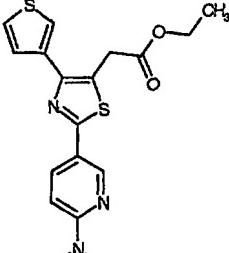
- 209 -

Table 42 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-------------------------|--------------------|---------------|---|
| 541                     |                    | Free material | Powder<br>MS·APCI (m/z) : 362/364 (M+H) + |
| 542                     |                    | Free material | Powder<br>MS·APCI (m/z) : 410/412 (M+H) + |
| 543                     |                    | Free material | Powder<br>MS·APCI (m/z) : 407/409 (M+H) + |
| 544                     |                    | Free material | Powder<br>MS·APCI (m/z) : 398/400 (M+H) + |

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Table 42 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 545                     |    | Free material | Powder<br>MS·APCI (m/z) : 398/400 (M+H) + |
| 546                     |   | Free material | Powder<br>MS·APCI (m/z) : 409/411 (M+H) + |
| 547                     |  | Free material | Powder<br>MS·APCI (m/z) : 395/397 (M+H) + |
| 548                     |  | Free material | Oil<br>MS·APCI (m/z) : 374 (M+H) +        |

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Table 42 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.               |
|-------------------------|--------------------|---------------|---------------------------------------|
| 549                     |                    | Free material | Powder<br>MS·APCI (m/z) : 375 (M+H) + |
| 550                     |                    | Free material | Oil<br>MS·APCI (m/z) : 348 (M+H) +    |
| 551                     |                    | Free material | Powder<br>MS·APCI (m/z) : 386 (M+H) + |
| 552                     |                    | Free material | Powder<br>MS·APCI (m/z) : 360 (M+H) + |

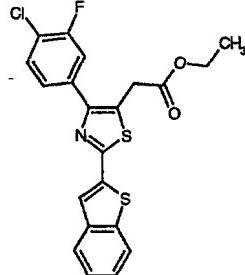
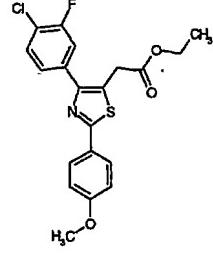
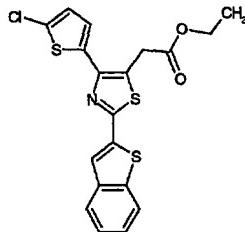
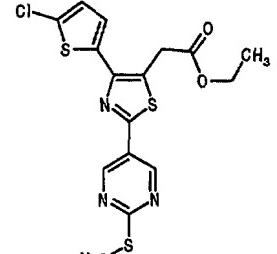
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Table 42 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-------------------------|--------------------|---------------|---|
| 553                     |                    | Free material | Oil<br>MS·APCI (m/z) : 360 (M+H) +        |
| 554                     |                    | Free material | Powder<br>MS·APCI (m/z) : 420/422 (M+H) + |
| 555                     |                    | Free material | Powder<br>MS·APCI (m/z) : 421/423 (M+H)   |
| 556                     |                    | Free material | Powder<br>MS·APCI (m/z) : 394/396 (M+H) + |

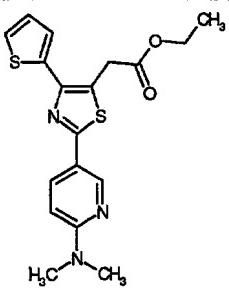
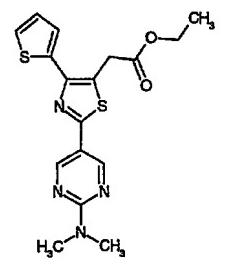
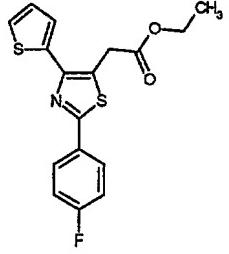
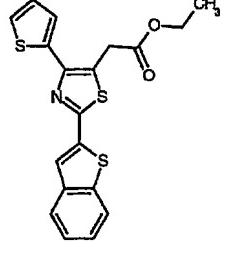
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Table 42 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 557                     |    | Free material | Powder<br>MS·APCI (m/z) : 432/434 (M+H) + |
| 558                     |   | Free material | Powder<br>MS·APCI (m/z) : 406/408 (M+H) + |
| 559                     |  | Free material | Powder<br>MS·APCI (m/z) : 420/422 (M+H) + |
| 560                     |  | Free material | Powder<br>MS·APCI (m/z) : 412/414 (M+H) + |

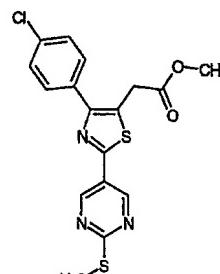
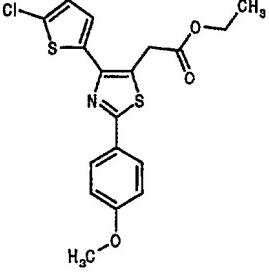
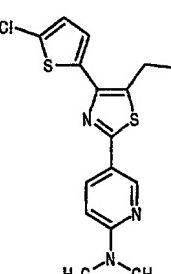
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Table 42 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.               |
|-------------------------|---|---------------|---------------------------------------|
| 561                     |    | Free material | Powder<br>MS·APCI (m/z) : 374 (M+H) + |
| 562                     |   | Free material | Powder<br>MS·APCI (m/z) : 375 (M+H) + |
| 563                     |  | Free material | Powder<br>MS·APCI (m/z) : 348 (M+H) + |
| 564                     |  | Free material | Powder<br>MS·APCI (m/z) : 386 (M+H) + |

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Table 42 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                   |
|-------------------------|---|---------------|---|
| 565                     |    | Free material | Powder<br>MS·APCI (m/z) : 392/394 (M+H) + |
| 566                     |   | Free material | Powder<br>MS·APCI (m/z) : 394/396 (M+H) + |
| 567                     |  | Free material | Powder<br>MS·APCI (m/z) : 408/410 (M+H) + |

## Preparation examples 568 to 597

5

The corresponding starting materials were hydrolyzed in the conventional manner to obtain the compounds shown in Table 43 below.

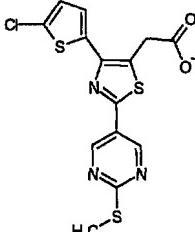
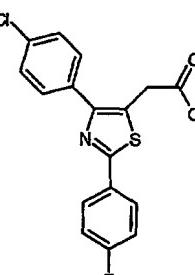
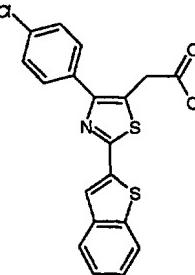
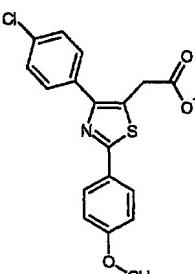
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Table 43

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 568                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>352/354 (M-Na) - |
| 569                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>390/392 (M-Na) - |
| 570                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>364/366 (M-Na) - |
| 571                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>378/380 (M-Na) - |

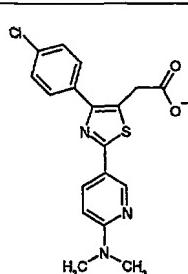
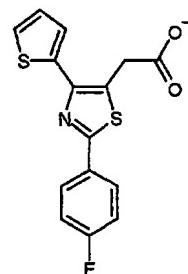
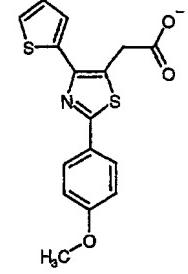
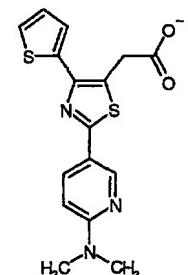
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Table 43 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 572                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>384/386 (M-Na) - |
| 573                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>346 (M-Na) -     |
| 574                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>384/386 (M-Na) - |
| 575                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>358/360 (M-Na) - |

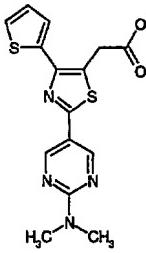
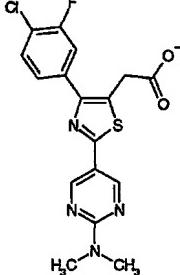
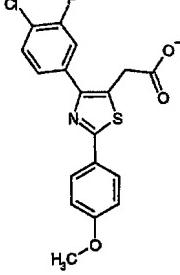
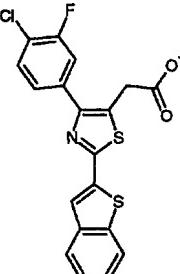
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Table 43 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                   |
|-------------------------|---|------|---|
| 576                     |    | Na   | Powder<br>ESI·MS (m/z) : 372/374 (M-Na) - |
| 577                     |   | Na   | Powder<br>ESI·MS (m/z) : 318 (M-Na) -     |
| 578                     |  | Na   | Powder<br>ESI·MS (m/z) : 330 (M-Na) -     |
| 579                     |  | Na   | Powder<br>ESI·MS (m/z) : 344 (M-Na) -     |

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Table 43 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                   |
|-------------------------|---|------|---|
| 580                     |    | Na   | Powder<br>ESI·MS (m/z) : 345 (M-Na) -     |
| 581                     |   | Na   | Powder<br>ESI·MS (m/z) : 391/393 (M-Na) - |
| 582                     |  | Na   | Powder<br>ESI·MS (m/z) : 376/378 (M-Na) - |
| 583                     |  | Na   | Powder<br>ESI·MS (m/z) : 358/360 (M-Na) - |

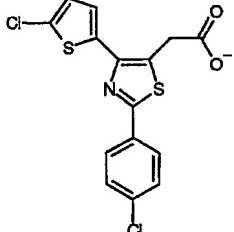
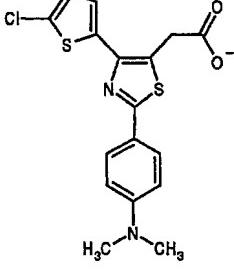
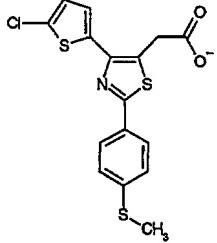
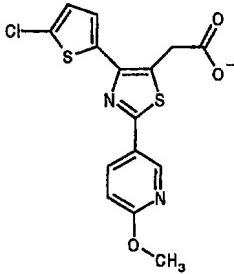
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Table 43 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 584                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>364/366 (M-Na) - |
| 585                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>390/392 (M-Na) - |
| 586                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>379/381 (M-Na) - |
| 587                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>368/370 (M-Na) - |

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Table 43 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 588                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>368/370 (M-Na) - |
| 589                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>377/379 (M-Na) - |
| 590                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>380/382 (M-Na) - |
| 591                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>365/367 (M-Na) - |

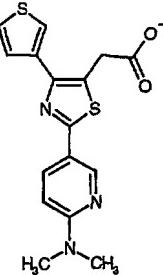
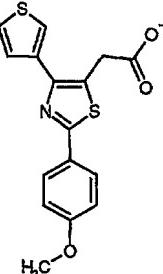
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Table 43 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                  |
|-------------------------|--------------------|------|--|
| 592                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>356 (M-Na) - |
| 593                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>356 (M-Na) - |
| 594                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>318 (M-Na) - |
| 595                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>345 (M-Na) - |

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Table 43 (contd.)

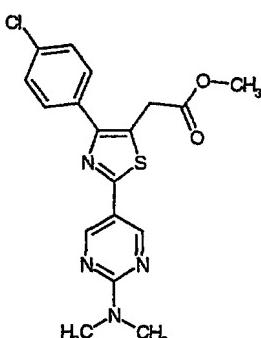
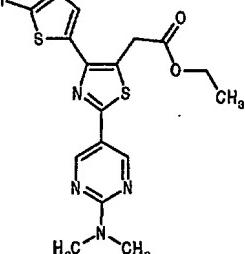
| Preparation example No. | Chemical structure   | Salt | Physical constant, etc.                  |
|-------------------------|--|------|--|
| 596                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>344 (M-Na) - |
| 597                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>330 (M-Na) - |

## 5 Preparation examples 598 to 599

The corresponding starting materials were treated in a manner similar to Preparation example 359 to obtain the compounds shown in Table 44 below.

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Table 44

| Preparation example No. | Chemical structure   | Salt          | Physical constant, etc.                   |
|-------------------------|--|---------------|---|
| 598                     |   | Free material | Powder<br>MS·APCI (m/z) : 389/391 (M+H) + |
| 599                     |  | Free material | Powder<br>MS·APCI (m/z) : 409/411 (M+H) + |

## Preparation examples 600 to 601

5

The corresponding starting materials were hydrolyzed in the conventional manner to obtain the compounds shown in Table 45 below.

10

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Table 45

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                      |
|-------------------------|--------------------|------|--|
| 600                     |                    | Na   | Powder<br>ESI-MS (m/z) :<br>379/381 (M-Na)   |
| 601                     |                    | Na   | Powder<br>ESI-MS (m/z) :<br>373/375 (M-Na) - |

## Preparation example 602

5

A mixture of ethyl 3-amino-4-(5-chlorothiophen-2-yl)-4-oxobutyrate hydrochloride (596 mg), 4-fluorobenzoyl chloride (380 mg) and sodium hydrogen carbonate (1.0 g) in ethyl acetate (10 ml) and water (10 ml) was stirred at room temperature for 10 2 hours. To the reaction mixture were added ethyl acetate (30 ml) and water (30 ml), and the organic layer was collected. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The resulting residue was triturated with 15 hexane to obtain a crude product of ethyl 4-(5-chlorothiophen-2-yl)-3-[(4-fluorobenzoyl)amino]-4-oxobutyrate (732 mg) as colorless powder.

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- A mixture of ethyl 4-(5-chlorothiophen-2-yl)-3-[(4-fluorobenzoyl)amino]-4-oxobutyrate (720 mg) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide (1.14 g) in tetrahydrofuran (20 ml) was refluxed for 2.5 hours.
- 5 The reaction mixture was cooled and purified by silica gel column chromatography (solvent: hexane : ethyl acetate= 20:1), and triturated with hexane to obtain ethyl 5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)thiazol-4-yl acetate (667 mg) as yellowish powder.
- 10 MS·APCI (m/z) : 382/284 (MH+)

**Preparation examples 603 to 607**

- The corresponding starting materials were treated in a manner
- 15 similar to Preparation example 602 to obtain the compounds shown in Table 46 below.

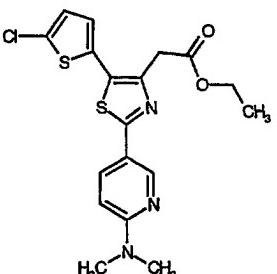
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Table 46

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                 |
|-------------------------|--------------------|---------------|---|
| 603                     |                    | Free material | Powder<br>MS·APCI(m/z) : 398/400(M+H) + |
| 604                     |                    | Free material | Powder<br>MS·APCI(m/z) : 420/422(M+H) + |
| 605                     |                    | Free material | Powder<br>MS·APCI(m/z) : 394/396(M+H) + |
| 606                     |                    | Free material | Powder<br>MS·APCI(m/z) : 409/411(M+H) + |

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Table 46 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                 |
|-------------------------|---|---------------|---|
| 607                     |  | Free material | Powder<br>MS·APCI(m/z) : 408/410 (M+H)+ |

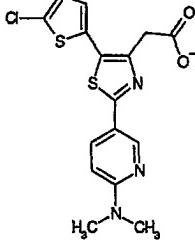
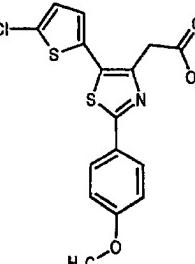
## Preparation examples 608 to 612

5

The corresponding starting materials were hydrolyzed in the conventional manner to obtain the compounds shown in Table 47 below.

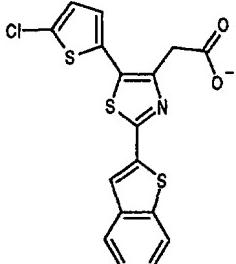
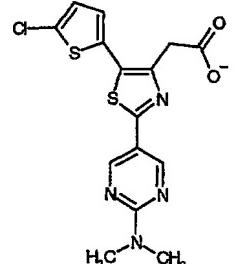
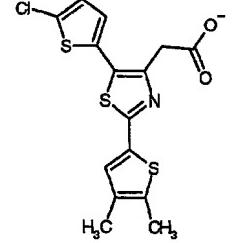
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Table 47

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                   |
|-------------------------|---|------|---|
| 608                     |  | Na   | Powder<br>ESI·MS (m/z) : 378/380 (M-Na) - |
| 609                     |  | Na   | Powder<br>ESI·MS (m/z) : 364/366 (M-Na) - |

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Table 47 (contd.)

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                      |
|-------------------------|---|------|--|
| 610                     |    | Na   | Powder<br>ESI·MS (m/z) :<br>390/392 (M-Na) - |
| 611                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>379/381 (M-Na) - |
| 612                     |  | Na   | Powder<br>ESI·MS (m/z) :<br>368/370 (M-Na) - |

## Preparation examples 613 to 622

5

In accordance with the above-mentioned preparation examples or the conventionally known preparation processes, the compounds shown in Table 48 below were obtained.

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Table 48

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.            |
|-------------------------|--------------------|---------------|------------------------------------|
| 613                     |                    | Free material |                                    |
| 614                     |                    | Na            | Powder<br>ESI·MS (m/z): 302 (M-Na) |
| 615                     |                    | Free material |                                    |
| 616                     |                    | Free material |                                    |

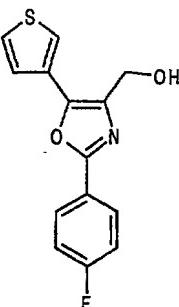
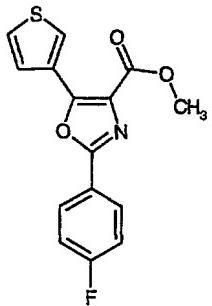
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Table 48 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                     |
|-------------------------|--------------------|---------------|---|
| 617                     |                    | Free material |   |
| 618                     |                    | Free material | Crystal<br>Melting point:<br>207-209°C      |
| 619                     |                    | Free material | Crystal<br>Melting point:<br>110-111°C      |
| 620                     |                    | Na            | Powder<br>ESI-MS (m/z):<br>328/330 (M-Na) - |

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Table 48 (contd.)

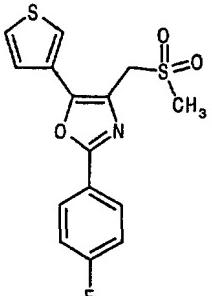
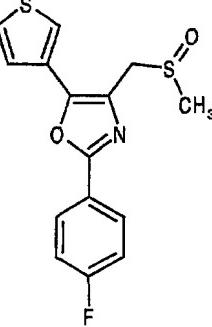
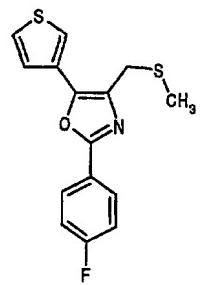
| Preparation example No. | Chemical structure   | Salt          | Physical constant, etc.                |
|-------------------------|--|---------------|--|
| 621                     |   | Free material | Powder                                 |
| 622                     |  | Free material | Crystal<br>Melting point:<br>213-214°C |

## 5 Preparation examples 623 to 631

According to the preparation example 129, 130, 135, 148, 152 or 330 mentioned above, the compounds shown in Table 49 below were obtained.

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Table 49

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.   |
|-------------------------|---|---------------|---|
| 623                     |    | Free material | Crystal<br>Melting point:<br>208-210°C<br>MS·APCI(m/z) :<br>338 (M+H) |
| 624                     |   | Free material | Crystal<br>Melting point:<br>173-174.5°C<br>MS·APCI(m/z) : 322 (M+H)  |
| 625                     |  | Free material | Crystal<br>Melting point:<br>111-112°C<br>MS·APCI(m/z) : 486 (M+H)    |

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Table 49 (contd.)

| Preparation example No. | Chemical structure | Salt | Physical constant, etc.                       |
|-------------------------|--------------------|------|---|
| 626                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>348/350 (M-Na) -  |
| 627                     |                    | Na   | Powder<br>ESI·MS (m/z) :<br>351/353 (M-Na) -  |
| 628                     |                    | Na   | Powder<br>MS·APCI (m/z) :<br>363/365 (M-Na) - |

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Table 49 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-------------------------|--------------------|---------------|---|
| 629                     |                    | Free material | Solid<br>MS·APCI (m/z) : 393/395 (M+H)    |
| 630                     |                    | Na            | Powder<br>ESI·MS (m/z) : 358/360 (M-Na) - |
| 631                     |                    | Na            | Powder<br>ESI·MS (m/z) : 359/361 (M-Na) - |

## Preparation example 632

5

(1) Ethyl 2-(4-chlorophenyl)-5-phenylthiazol-4-yl acetate (4.5 g) was dissolved in methanol (50 ml), and ammonia was saturated in the solution at 0°C and the resulting mixture was allowed to stand at room temperature for 3 days. After removing the solvent, methanol was added to the residue. The resulting

10

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precipitate was collected and dried to obtain 2-(4-chlorophenyl)-5-phenylthiazol-4-yl acetamide (4.2 g).

Melting point: 202-203°C

MS·EI (m/z): 328 (M+)

5

(2) To a solution of 2-(4-chlorophenyl)-5-phenylthiazol-4-yl acetamide (3.4 g) and phosphorus oxychloride (3 ml) in chloroform (50 ml) was added one drop of pyridine, and the mixture was refluxed for 8 hours. Cold diluted aqueous ammonia was poured into the mixture and the organic layer was collected. After removing the solvent under reduced pressure, ethanol was added to the residue and crystal was collected by filtration to obtain 2-(4-chlorophenyl)-5-phenylthiazol-4-yl acetonitrile (3.1 g).

Melting point: 118-120°C

15 MS·EI (m/z): 310 (M+)

(3) To a solution of 2-(4-chlorophenyl)-5-phenylthiazol-4-yl acetonitrile (2.33 g) in N,N-dimethylformamide (30 ml) were added sodium azide (1.40 g) and ammonium chloride (1.3 g), and the mixture was stirred at 90°C for 12 hours. After removing the solvent under reduced pressure, ethyl acetate and water were added to the residue. The organic layer was collected, dried and the solvent was removed under reduced pressure. The residue was recrystallized from chloroform and methanol to obtain 25 5-[2-(4-chlorophenyl)-5-phenyl-thiazol-4-ylmethyl]tetrazole (1.75 g).

Melting point: 213-214°C

MS·EI (m/z): 353 (M+)

30 Preparation examples 633 to 641

The corresponding starting materials were treated in a manner similar to Preparation example 43, 135, 608 or the conventionally known processes to obtain the compounds shown in Table 50 below.

35

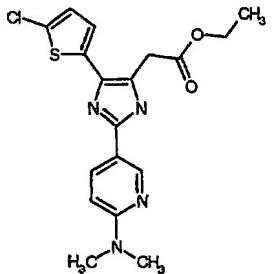
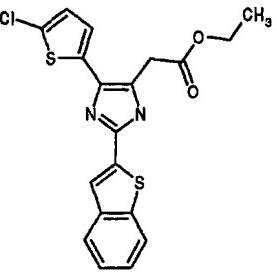
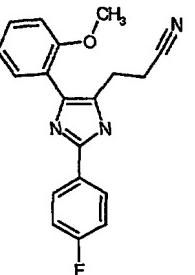
- 237 -

Table 50

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-------------------------|--------------------|---------------|---|
| 633                     |                    | Free material | Solid<br>MS·APCI (m/z) : 397/399 (M+H) +  |
| 634                     |                    | Free material | Powder<br>MS·APCI (m/z) : 392/394 (M+H) + |
| 635                     |                    | Free material | Powder<br>MS·APCI (m/z) : 377/379 (M+H) + |

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Table 50 (contd.)

| Preparation example No. | Chemical structure  | Salt          | Physical constant, etc.                     |
|-------------------------|---|---------------|---|
| 636                     |    | Free material | Powder<br>MS·APCI(m/z) :<br>391/393 (M+H) + |
| 637                     |   | Free material | Powder<br>MS·APCI(m/z) :<br>402/404 (M+H) + |
| 638                     |  | Free material | Powder<br>MS·APCI(m/z) :<br>308 (MH+)       |

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Table 50 (contd.)

| Preparation example No. | Chemical structure | Salt          | Physical constant, etc.  |
|-------------------------|--------------------|---------------|--|
| 639                     |                    | 1HCl          | Crystal<br>Melting point:<br>203-204°C<br>EI·MS (m/z) :<br>298 (M'-16) + |
| 640                     |                    | Na            | Powder<br>ESI·MS (m/z) :<br>352 (M-Na)                                   |
| 641                     |                    | Free material |  |

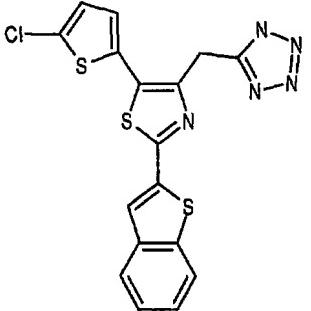
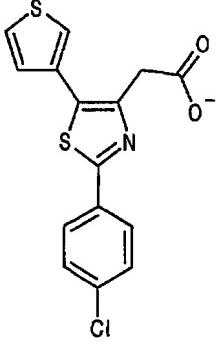
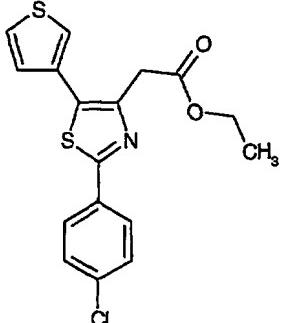
## Reference Examples 642 to 644

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The following compounds listed in Table 50a were prepared in a manner similar to Example 608 or 632, or similar to that described in Japanese Provisional Patent Publication No. 167685/1986.

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Table 50a

| Preparation example No. | Chemical structure  | Salt | Physical constant, etc.                     |
|-------------------------|---|------|---|
| 642                     |    | Free | Powder<br>ESI·MS (m/z) :<br>414/416 (M-H) - |
| 643                     |   | Na   | Powder<br>ESI·MS (m/z) :<br>334 (M-Na) -    |
| 644                     |  | Free |   |

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Reference example 1

(1) A mixture of 2-acetylpyrimidine (2.90 g), hydroxylamine hydrochloride (2.48 g) and triethylamine (5.3 ml) in ethanol (40 ml) was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with methylene chloride. The organic layer was washed with a saturated aqueous ammonium sulfate solution and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to obtain 2-acetylpyrimidine oxime (4.44 g) as colorless powder.

MS·APCI (m/z): 138 (MH+)

(2) A mixture of 2-acetylpyrimidine oxime (4.40 g) and p-toluenesulfonyl chloride (6.79 g) in pyridine (40 ml) was stirred at room temperature overnight. The reaction mixture was poured into ice-water and precipitated crude product was collected by filtration. The filtrate was neutralized by 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue and the crude product previously obtained were combined and triturated with diethyl ether to obtain O-p-toluenesulfonyl-2-acetylpyrimidine oxime (4.53 g) as colorless powder.

(3) To ice-cooled ethanol (19 ml) was added sodium hydride (681 mg, 60% mineral oil) and the mixture was stirred at room temperature for 30 minutes. To the solution was added dropwise a solution of O-p-toluenesulfonyl-2-acetylpyrimidine oxime (4.51 g) in ethanol (16 ml) and of tetrahydrofuran (10 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for 1.5 hours. To the reaction mixture was added diethyl ether (150 ml) and precipitated insoluble material was removed by filtration. The filtrate was extracted with 2N hydrochloric acid and the aqueous layer was concentrated under reduced pressure. The resulting residue was triturated with

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acetone-ethanol to obtain 2-(2-aminoacetyl)pyrimidine hydrochloride (2.87 g) as pale brownish powder.

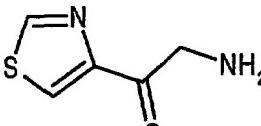
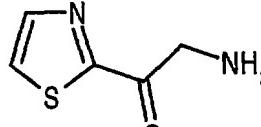
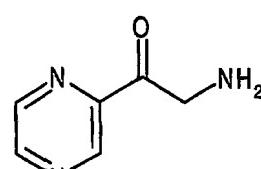
MS·APCI (m/z) : 138 (MH<sup>+</sup>)

5 Reference examples 2 to 4

Corresponding starting compounds were treated in a manner similar to Reference example 1 to obtain the compounds shown in Table 51 below.

10

Table 51

| Reference example No. | Chemical structure  | Salt | Physical constant, etc.                          |
|-----------------------|---|------|--|
| 2                     |   | 1HCl | Powder<br>MS·APCI (m/z) : 143 (M+H) <sup>+</sup> |
| 3                     |  | 1HCl | Powder<br>MS·APCI (m/z) : 143 (M+H) <sup>+</sup> |
| 4                     |  | 1HCl | Powder<br>MS·APCI (m/z) : 138 (M+H) <sup>+</sup> |

## Reference example 5

- (1) To a solution of 1-(3-pyridyl)-1-butanone (20.0 g) in 47% aqueous hydrobromic acid (40 ml) and acetic acid (40 ml) was 5 added bromine (15.2 ml), and the mixture was stirred at 60°C for 30 minutes. The reaction mixture was poured into ice-water, and after adding a saturated aqueous sodium thiosulfate solution, potassium carbonate was added to the mixture to adjust pH to 4. The reaction mixture was extracted with ethyl acetate, washed 10 successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain a crude product of 2-bromo-1-(3-pyridyl)-1-butanone (30.15 g) as brownish oil.
- 15 (2) The crude product obtained in the above (1) was dissolved in N,N-dimethylformamide (100 ml), and sodium azide (9.50 g) was added to the solution under ice-cooling and the resulting mixture was stirred at room temperature for one hour. Water 20 was added to the reaction mixture, the mixture was extracted with ethyl acetate three times, and combined organic layers was washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel flush column chromatography (solvent: 25 n-hexane : ethyl acetate=2:1) to obtain 2-azido-1-(3-pyridyl)-1-butanone (18.65 g) as yellowish oil.
- MS·APCI (m/z): 191 (MH+)
- (3) A mixture of 2-azido-1-(3-pyridyl)-1-butanone (18.60 g), 30 di-t-butyl dicarbonate (23.50 g) and 10% palladium-carbon (2.70 g) in methanol (200 ml) was stirred under hydrogen atmosphere at room temperature for one hour. After removing the palladium-carbon by filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel flush 35 column chromatography (solvent: hexane : ethyl acetate= 2:1→1:1) to obtain 2-(t-butoxycarbonylamino)-1-(3-pyridyl)-

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1-butanone (20.53 g) as yellowish red oil.

- (4) A mixture of 2-(t-butoxycarbonylamino)-1-(3-pyridyl)-1-butanone (20.50 g) and 6N hydrochloric acid (38.8 ml) in ethanol (100 ml) was refluxed for one hour. After cooling, the reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with ethanol-ethyl acetate (1:1) to obtain 2-amino-1-(3-pyridyl)-1-butanone dihydrochloride (13.40 g) as pale reddish purple crystalline powder.
- 10 Melting point: 199 to 201°C (decomposed)

Reference examples 6 to 8

- Corresponding starting compounds were treated in a manner similar  
15 to Reference example 5 to obtain the compounds shown in Table  
52 below.

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Table 52

| Reference example No. | Chemical structure | Salt | Physical constant, etc.  |
|-----------------------|--------------------|------|--|
| 6                     |                    | 1HCl | Powder<br>MS·APCI (m/z) :<br>184 (M+H) +                                 |
| 7                     |                    | 1HCl | Crystal<br>Melting point:<br>156-158°C<br>MS·APCI (m/z) :<br>178 (M+H) + |
| 8                     |                    | 1HCl | Powder<br>MS·APCI (m/z) :<br>164 (M+H) +                                 |

## Reference example 9

5

To a solution of an acid chloride product prepared from 6-methyl nicotinic acid (245 mg) in chloroform (10 ml) were added 2-amino-1-(3-pyridyl)-1-butanone dihydrochloride (356 mg) and triethylamine (1.05 ml), and the mixture was stirred for 30

10 minutes. The mixture was poured into water and extracted with ethyl acetate. The organic layer was collected, washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain a crude product of

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2-(6-methylnicotynoylamino)-1-(3-pyridyl)-1-butanone (425 mg).

Reference example 10

5

(1) A mixture of 3-(2-aminoacetyl)pyridine dihydrochloride (50.00 g), 4-fluorobenzoyl chloride (41.71 g) and sodium hydrogen carbonate (100.44 g) in ethyl acetate (1 liter) and water (0.6 liter) was stirred at room temperature for 2 hours. To the reaction mixture were added tetrahydrofuran (0.5 liter) and water (1 liter), and the organic layer was collected. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The resulting residue was triturated with ethyl acetate to obtain 3-[2-(4-fluorobenzoyl)aminoacetyl]pyridine (40.87 g) as pale yellowish powder.

Melting point: 164.5 to 165.5°C

MS·APCI (m/z): 259 (MH<sup>+</sup>)

20 (2) To a solution of 3-[2-(4-fluorobenzoyl)aminoacetyl]-pyridine (500 mg) in N,N-dimethylformamide (10 ml) were added sodium hydride (81.3 mg, 60% mineral oil) and acrylonitrile (113 mg) under dry ice-acetone cooling, and the mixture was stirred at the same temperature under argon atmosphere for 10 minutes.

25 The mixture was warmed slowly to 0°C and stirred at the same temperature for 30 minutes. To the reaction mixture was added a saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain a crude product of 4-cyano-2-(4-fluorobenzoylamino)-1-(3-pyridyl)-1-butanone (500 mg).

Reference example 11

35

(1) To acetic anhydride (2.39 ml) was added dropwise formic

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acid (0.97 ml) under ice-cooling, and the mixture was stirred at 50°C for 30 minutes. The mixture was ice-cooled again, and diluted with tetrahydrofuran (9 ml). To the mixture were added 2-amino-1-(3-pyridyl)-1-butanone dihydrochloride (600 mg) and 5 triethylamine (1.41 ml), and the mixture was stirred under ice-cooling for 1.5 hours. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and 10 the solvent was removed under reduced pressure. The resulting residue was triturated with ethyl acetate-diethyl ether to obtain 2-formylamino-1-(3-pyridyl)-1-butanone (440 mg) as colorless powder.

MS·APCI (m/z): 193 (MH+)

15 (2) A mixture of 2-formylamino-1-(3-pyridyl)-1-butanone (640 mg) and ammonium acetate (5.13 g) in acetic acid (5 ml) was stirred at 100°C for 1.5 hours. After cooling, 28% aqueous ammonia was added to the reaction mixture and the mixture was extracted with 20 chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was triturated with ethyl acetate-diethyl ether to obtain 5-ethyl-4-(3-pyridyl)imidazole (520 mg) as colorless powder.

25 MS·APCI (m/z): 174 (MH+)

(3) To a solution of 5-ethyl-4-(3-pyridyl)imidazole (1.50 g) and potassium acetate (2.55 g) in methanol (40 ml) was added iodine (2.86 g), and the mixture was stirred at room temperature 30 overnight. To the reaction mixture were added water and ethyl acetate, and the organic layer was collected, washed with a saturated aqueous sodium thiosulfate solution and brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by NH 35 silica gel flush column chromatography (solvent: ethyl acetate) to obtain 5-ethyl-2-iodo-4-(3-pyridyl)imidazole (1.75 g).

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MS·APCI (m/z) : 300 (MH+)

Reference example 12

- 5       (1) A mixture of methyl  $\alpha$ -amino-2-thiophene acetate (1.48 g),  
4-fluorobenzoyl chloride (1.64 g) and sodium hydrogen carbonate  
(2.89 g) in methylene chloride (20 ml) and water (20 ml) was  
stirred at room temperature overnight. The organic layer was  
collected, washed with water and brine, and the solvent was  
10 removed under reduced pressure. The resulting residue was  
triturated with ethyl acetate-hexane to obtain methyl  
 $\alpha$ -(4-fluorobenzoylamino)-2-thiophene acetate (2.40 g) as  
colorless powder.

MS·APCI (m/z) : 294 (MH+)

- 15       (2) To a solution of diisopropylamine (2.48 g) in tetrahydrofuran  
(45 ml) was added dropwise 1.6M n-butyl lithium (15.71 ml,  
n-hexane solution) under argon atmosphere at -78°C, and after  
stirring for 30 minutes, a solution of ethyl acetate (2.16 g)  
20 in tetrahydrofuran (5 ml) was added dropwise to the mixture and  
the resulting mixture was further stirred for 30 minutes. To  
the mixture was slowly added a solution of methyl  $\alpha$ -(4-  
fluorobenzoylamino)-2-thiophene acetate (2.40 g) in  
tetrahydrofuran (15 ml), and the mixture was stirred for one  
25 hour. To the reaction mixture were added a saturated aqueous  
ammonium chloride solution and the mixture was extracted with  
ethyl acetate. The organic layer was washed with water and brine,  
dried over anhydrous sodium sulfate and the solvent was removed  
under reduced pressure. The resulting residue was purified by  
30 silica gel flush column chromatography (solvent: chloroform :  
ethanol=100:1) to obtain ethyl 4-(4-fluorobenzoylamino)-4-  
(2-thienyl)acetacetate (2.53 g) as yellowish oil.

MS·APCI (m/z) : 350 (MH+)

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Reference example 13

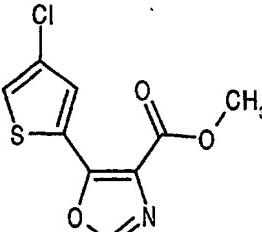
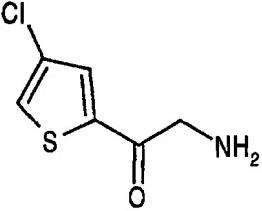
- (1) To a solution of benzo[b]furan-5-carboxylic acid (1.30 g) and of methyl isocyanoacetate (834 mg) in N,N-dimethylformamide (10 ml) were added diethyl cyanophosphate (1.33 ml) and triethylamine (3.6 ml) at room temperature, and the mixture was stirred overnight. After removing the solvent under reduced pressure, an aqueous citric acid solution and ethyl acetate were added to the residue, the organic layer was collected, washed successively with an aqueous citric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: n-hexane : ethyl acetate=1:1) to obtain a crude product of methyl 5-(5-benzo[b]furyl)oxazol-4-carboxylate (1.14 g).
- (2) To a solution of the crude product of methyl 5-(5-benzo[b]furyl)oxazol-4-carboxylate (1.14 g) in methanol (20 ml) and tetrahydrofuran (5 ml) was added conc. hydrochloric acid (8 ml), and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with methanol-diethyl ether-acetone to obtain 5-(aminoacetyl)benzo[b]furan hydrochloride (600 mg).
- MS·APCI (m/z): 176 (MH<sup>+</sup>)

Reference example 14

- Corresponding starting compounds were treated in a manner similar to Reference example 13(1) and (2) to obtain the compounds shown in Table 53 below.

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Table 53

| Reference example No. | Chemical structure   | Salt          | Physical constant, etc.                  |
|-----------------------|--|---------------|--|
| 14(1)                 |   | Free material | Solid<br>MS·APCI (m/z) :<br>244 (M+H) +  |
| 14(2)                 |  | 1HCl          | Powder<br>MS·APCI (m/z) :<br>176 (M+H) + |

## 5 Reference examples 15 to 19

Corresponding starting compounds were treated in a manner similar to Reference example 10(1) to obtain the compounds shown in Table 54 below.

Table 54

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-----------------------|--------------------|---------------|---|
| 15                    |                    | Free material | Powder<br>MS·APCI (m/z) : 298 (M+H) +     |
| 16                    |                    | Free material | Powder<br>MS·APCI (m/z) : 298 (M+H) +     |
| 17                    |                    | Free material | Powder<br>MS·APCI (m/z) : 320 (M+H) +     |
| 18                    |                    | Free material | Powder<br>MS·APCI (m/z) : 320 (M+H) +     |
| 19                    |                    | Free material | Powder<br>MS·APCI (m/z) : 281/283 (M+H) + |

## 5 Reference example 20

(1) To a solution of 2-chloro-5-(bromoacetyl)thiophene (28.04 g) in acetonitrile (150ml) was added sodium diformylimide (13.35 g), and the mixture was stirred at room temperature for 45 minutes

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followed by stirring at 50°C for 2.5 hours. The reaction mixture was filtered through Celite, insoluble material was washed with tetrahydrofuran, the filtrate and the washed solution were combined and the solvent was removed under reduced pressure.

- 5 The residue was crystallized from diisopropyl ether to obtain a crude crystal of 2-chloro-5-(diformylaminoacetyl)thiophene (20.63 g).

(2) To the crude crystal of 2-chloro-5-(diformylaminoacetyl)-  
10 thiophene were added potassium hydroxide (0.60 g), ethanol (70 ml) and tetrahydrofuran (40 ml), and the mixture was stirred at room temperature for one hour. After removing the solvent under reduced pressure, tetrahydrofuran (150 ml) and anhydrous magnesium sulfate were added to the residue, and insoluble  
15 material was removed by filtration and washed with tetrahydrofuran. The filtrate and the washed solution were combined and the solvent was removed under reduced pressure. The residue was crystallized from diisopropyl ether-ethyl acetate to obtain 2-chloro-5-(formylaminoacetyl)thiophene (14.81 g) as pale  
20 brownish crystal.

Melting point: 111 to 113°C

MS·APCI (m/z): 204 (MH+)

(3) To a solution of 2-chloro-5-(formylaminoacetyl)thiophene  
25 (20.1 g) in N,N-dimethylformamide (400 ml) was added sodium hydride (4.44 g, 60% mineral oil) under ice-cooling, and the mixture was stirred under argon atmosphere at room temperature for one hour. After ice-cooling, to the mixture was added dropwise ethyl bromoacetate (20.8 g), and the mixture was stirred  
30 at room temperature for 2 hours. After cooling, ice was added to the reaction mixture, and then water and ethyl acetate were also added to the mixture. The organic layer was collected, washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The  
35 resulting residue was purified by silica gel column chromatography (solvent: n-hexane : ethyl acetate=6:1) to obtain

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ethyl 4-(5-chlorothiophen-2-yl)-3-formylamino-4-oxobutyrate  
(17.8 g) as yellowish oil.

MS·APCI (m/z) : 290/292 (MH<sup>+</sup>)

- 5 (4) To a solution of 4-(5-chlorothiophen-2-yl)-3-formyl-  
amino-4-oxobutyrate (17.8 g) in ethanol (178 ml) was added 4N  
hydrogen chloride-dioxane solution (178 ml) under ice-cooling,  
and the mixture was stirred at room temperature for 18 hours.  
After completion of the reaction, the solvent was removed under  
10 reduced pressure, and the resulting residue was triturated with  
ethyl acetate to obtain ethyl 4-(5-chlorothiophen-2-yl)-3-  
amino-4-oxobutyrate hydrochloride (14.2 g) as colorless powder.  
MS·APCI (m/z) : 262/264 (MH<sup>+</sup>)

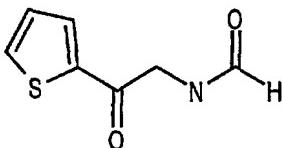
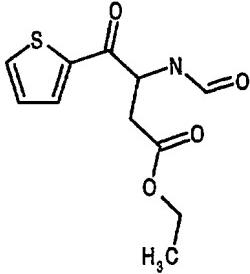
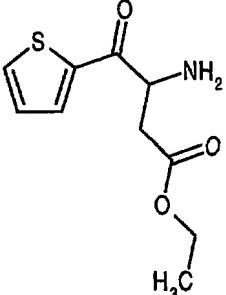
15 Reference example 21

Corresponding starting compounds were treated in a manner similar  
to Reference example 20(1) to (4) to obtain the compounds shown  
in Table 55 below.

20

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Table 55

| Reference example No. | Chemical structure  | Salt          | Physical constant, etc.               |
|-----------------------|---|---------------|---------------------------------------|
| 21(1)                 |    | Free material | Powder<br>MS·APCI (m/z) : 170 (M+H) + |
| 21(2)                 |   | Free material | Powder<br>MS·APCI (m/z) : 256 (M+H) + |
| 21(3)                 |  | 1HCl          | Powder<br>MS·APCI (m/z) : 228 (M+H) + |

## Reference example 22

5

- (1) A mixed solution of  $\beta$ -methyl N-(5-benzo[b]furoyl)aspartate (1.0 g) and acetic anhydride (10 ml) was stirred at 85°C for one hour. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was crystallized from n-hexane-diethyl ether to obtain 2-(5-benzo[b]furyl)-4-methoxycarbonylmethyl-5-oxo-2-oxazoline (751 mg) as colorless powder.

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(2) To a mixture of 2-(5-benzo[b]furyl)-4-methoxycarbonyl-methyl-5-oxo-2-oxazoline (410 mg) and 3-thienoyl chloride (242 mg) in ethyl acetate (8 ml) was added triethyl amine (0.23 ml) under ice-cooling, and the mixture was stirred at room 5 temperature for 0.5 hour. Ethyl acetate was added to the mixture, the mixture was filtered and the resulting filtrate was concentrated under reduced pressure. A mixture of the resulting residue and pyridine (3.6 ml) was stirred at room temperature for 10 minutes followed by stirring at 60°C for 2 hours. Then, 10 acetic acid (1.35 ml) was added to the mixture and the resulting mixture was stirred at 80°C for 1.5 hours. After cooling, to the reaction mixture were added water and ethyl acetate, the organic layer was collected, washed successively with a 10% aqueous hydrochloric acid solution, a saturated aqueous sodium 15 hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=5:1) to obtain methyl 3-(5-benzo[b]furoylamino)-4-(3-thienyl)-4- 20 oxobutyrate (253 mg) as colorless powder.

MS·APCI (m/z): 358 (MH<sup>+</sup>)

Reference example 23

25 Corresponding starting compounds were treated in a manner similar to Reference example 10(1) to obtain 2-[2-(4-fluorobenzoyl-amino)acetyl]thiophene.

Reference example 24

30 (1) To a solution of methyl 5-(5-chlorothiophen-2-yl)oxazol-4-carboxylate (12.6 g) in methanol (150 ml) was added 4N hydrogen chloride-dioxane solution (100 ml) under argon atmosphere, and the mixture was stirred at 70°C for overnight. The reaction 35 mixture was cooled and the solvent was removed under reduced pressure, and the resulting residue was triturated with acetone

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to obtain methyl 2-amino-3-(5-chlorothiophen-2-yl)-3-oxo-propionate hydrochloride (13.9 g) as colorless powder.

MS·APCI (m/z) : 234 (MH<sup>+</sup>)

- 5     (2) A mixture of methyl 2-amino-3-(5-chlorothiophen-2-yl)-3-oxopropionate hydrochloride (6.0 g), 4-fluorobenzoyl chloride (4.23 g) and sodium hydrogen carbonate (11.2 g) in ethyl acetate (100 ml) and water (10 ml) was stirred at room temperature for 2 hours. The organic layer was collected, washed with water  
10    and brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The resulting residue was triturated with diethyl ether to obtain methyl 3-(5-chlorothiophen-2-yl)-2-(4-fluorobenzoylamino)-3-oxopropionate (7.3 g) as colorless powder.  
15    MS·APCI (m/z) : 356/358 (MH<sup>+</sup>)

Reference example 25

- 20    A mixture of 1,2,3,4-tetrahydroquinolin-6-carboxylic acid (2 g), 32% aqueous formalin solution (2 ml) and 10% palladium-carbon (400 mg) in N,N-dimethylformamide (10 ml) was stirred under hydrogen atmosphere at room temperature for one hour. After removing the palladium-carbon by filtration, the solvent was removed under reduced pressure and the resulting residue was  
25    triturated with diethyl ether to obtain 1-methyl-1,2,3,4-tetrahydroquinolin-6-carboxylic acid (1.98 g) as yellowish powder.

ESI·MS (m/z) : 190 (M-H)<sup>-</sup>

- 30    Reference example 26

Corresponding starting compounds were treated in a manner similar to Reference example 25 to obtain 1-methylindolin-5-carboxylic acid.

- 35    ESI·MS (m/z) : 176 (M-H)<sup>-</sup>

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Reference example 27

A mixture of methyl 6-methoxymethylnicotinate (737 mg) in a 2N aqueous sodium hydroxide solution (2 ml) and methanol (15 ml) 5 was refluxed overnight. After cooling, the reaction mixture was concentrated under reduced pressure, and the resulting residue was triturated with diethyl ether to obtain 6-methoxymethylnicotinic acid sodium salt (754 mg) as colorless powder.

10 ESI·MS (m/z): 166 (M-Na)

Reference example 28

(1) To a solution of methyl 6-bromomethylnicotinate (350 mg) 15 in tetrahydrofuran (5 ml) was added a 50% aqueous dimethylamine solution (3 ml), and the mixture was vigorously stirred at room temperature for 10 minutes. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over 20 anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: chloroform : methanol= 100:1) to obtain methyl 6-(dimethylamino)methylnicotinate (276 mg) as brownish powder.

25 MS·APCI (m/z): 195 (MH+)

(2) A mixture of methyl 6-(dimethylamino)methylnicotinate (256 mg) and 10N hydrochloric acid was refluxed overnight. After 30 cooling, the reaction mixture was concentrated under reduced pressure to obtain 6-(dimethylamino)methylnicotinic acid hydrochloride (329 mg) as colorless powder.

MS·APCI (m/z): 181 (MH+)

## Reference example 29

To a suspension of 3-(2-aminoacetyl)pyridine dihydrochloride (5.23 g) in chloroform (50 ml) were added di-t-butyl dicarbonate (5.73 g) and triethylamine (10.5 ml), and the mixture was stirred for one hour. Water was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and active charcoal was added thereto and insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by medium pressure column chromatography (solvent: chloroform : methanol=30:1→20:1), and triturated with diisopropyl ether to obtain 3-(2-t-butoxycarbonylaminocetyl)pyridine (3.20 g).

15 Melting point: 98 to 99°C  
MS·APCI (m/z): 237 (MH<sup>+</sup>)

## Reference example 30

20 (1) A mixture of (2-methoxy)phenacyl bromide (550 mg) and sodium diformylimide (274 mg) in acetonitrile (2.5 ml) was stirred at room temperature for 30 minutes, and then, stirred at 70°C for 24 hours. Insoluble material was removed by filtration, washed with acetonitrile and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=2:1), and triturated with hexane-ethyl acetate to obtain 2-(diformylamino)-2'-methoxyacetophenone (4.40 g) as colorless powder.

25 (2) A mixture of 2-(diformyl-amino)-2'-methoxyacetophenone (3.28 g) and 5% hydrogen chloride-ethanol solution (37 ml) was stirred at room temperature for 17 hours. The reaction mixture was concentrated under reduced pressure and the residue was triturated with diethyl ether. To the powder was again added 30 5% hydrogen chloride-ethanol solution and the mixture was stirred at room temperature for one day, and the mixture was concentrated

35

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under reduced pressure. The residue was washed with diethyl ether and ethyl acetate to obtain 2-amino-2'-methoxyaceto-phenone hydrochloride (2.91 g) as colorless solid.

MS·APCI (m/z): 166 (MH<sup>+</sup>)

5

Reference example 31

A mixture of methyl dl- $\alpha$ -amino-2-thiophene acetate (5.59 g), N-chlorosuccinimide (4.67 g) and acetic acid (60 ml) was stirred 10 at room temperature overnight. The reaction mixture was concentrated under reduced pressure, to the residue obtained was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under 15 reduced pressure. To the resulting residue were added methanol (40 ml) and 4N hydrogen chloride-dioxane solution (30 ml), the solvent was removed under reduced pressure and the residue was triturated with using diethyl ether and methanol to obtain methyl dl- $\alpha$ -amino-2-(5-chlorothiophene)acetate hydrochloride (4.24 20 g) as pale brownish powder.

MS·APCI (m/z): 206/208 (MH<sup>+</sup>)

Reference examples 32 to 46

25 Corresponding starting compounds were treated in a manner similar to Reference example 12(1) to obtain the compounds shown in Table 56 below.

Table 56

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-----------------------|--------------------|---------------|---|
| 32                    |                    | Free material | Powder<br>MS·APCI (m/z) : 360/362 (M+H) + |
| 33                    |                    | Free material | Powder<br>MS·APCI (m/z) : 349/351 (M+H) + |
| 34                    |                    | Free material | Powder<br>MS·APCI (m/z) : 348/350 (M+H) + |
| 35                    |                    | Free material | Powder<br>MS·APCI (m/z) : 360/362 (M+H) + |
| 36                    |                    | Free material | Powder<br>MS·APCI (m/z) : 355/357 (M+H) + |

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Table 56 (contd.)

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-----------------------|--------------------|---------------|---|
| 37                    |                    | Free material | Powder<br>MS·APCI (m/z) : 340/342 (M+H) + |
| 38                    |                    | Free material | Powder<br>MS·APCI (m/z) : 335/336 (M+H) + |
| 39                    |                    | Free material | Powder<br>MS·APCI (m/z) : 321 (M+H) +     |
| 40                    |                    | Free material | Powder<br>MS·APCI (m/z) : 332 (M+H) +     |
| 41                    |                    | Free material | Powder<br>MS·APCI (m/z) : 321 (M+H) +     |

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Table 56 (contd.)

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                 |
|-----------------------|--------------------|---------------|---|
| 42                    |                    | Free material | Powder<br>MS·APCI (m/z) : 306 (M+H) +   |
| 43                    |                    | Free material | Powder<br>MS·APCI (m/z) : 320 (M+H) +   |
| 44                    |                    | Free material | Powder<br>MS·APCI (m/z) : 332 (M+H) +   |
| 45                    |                    | Free material | Powder<br>MS·APCI (m/z) : 366/368 (M+H) |
| 46                    |                    | Free material | Oil<br>MS·APCI (m/z) : 354/356 (M+H) +  |

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Reference examples 47 to 61

Corresponding starting compounds were treated in a manner similar  
to Reference example 12(2) to obtain the compounds shown in Table  
5 57 below.

Table 57

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-----------------------|--------------------|---------------|---|
| 47                    |                    | Free material | Powder<br>MS·APCI (m/z) : 390/392 (M+H) + |
| 48                    |                    | Free material | Powder<br>MS·APCI (m/z) : 396/398 (M+H) + |
| 49                    |                    | Free material | Powder<br>MS·APCI (m/z) : 377 (M+H) +     |
| 50                    |                    | Free material | Powder<br>MS·APCI (m/z) : 388 (M+H) +     |
| 51                    |                    | Free material | Powder<br>MS·APCI (m/z) : 377 (M+H) +     |

Table 57 (contd.)

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.   |
|-----------------------|--------------------|---------------|---|
| 52                    |                    | Free material | Powder<br>MS·APCI (m/z) : 376 (M+H) +                                   |
| 53                    |                    | Free material | Powder<br>MS·APCI (m/z) : 388 (M+H) +                                   |
| 54                    |                    | Free material | Oil<br>MS·APCI (m/z) : 362 (M+H) +                                      |
| 55                    |                    | Free material | Powder<br>MS·APCI (m/z) : 422/424 (M+H) +                               |
| 56                    |                    | Free material | Crystal<br>Melting point: 126-128 °C<br>MS·APCI (m/z) : 410/412 (M+H) + |

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Table 57 (contd.)

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-----------------------|--------------------|---------------|---|
| 57                    |                    | Free material | Powder<br>MS·APCI (m/z) : 416/418 (M+H) + |
| 58                    |                    | Free material | Powder<br>MS·APCI (m/z) : 411/413 (M+H) + |
| 59                    |                    | Free material | Powder<br>MS·APCI (m/z) : 405/407 (M+H) + |
| 60                    |                    | Free material | Powder<br>MS·APCI (m/z) : 404/406 (M+H) + |
| 61                    |                    | Free material | Powder<br>MS·APCI (m/z) : 378/380 (M+H) + |

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## Reference examples 62 to 66

Corresponding starting compounds were treated in a manner similar to Reference example 10(1) to obtain the compounds shown in Table 5 58 below.

Table 58

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                   |
|-----------------------|--------------------|---------------|---|
| 62                    |                    | Free material | Powder<br>MS·APCI (m/z) : 259 (M+H)       |
| 63                    |                    | Free material | Powder<br>MS·APCI (m/z) : 340/342 (M+H) + |
| 64                    |                    | Free material | Powder<br>MS·APCI (m/z) : 348/350 (M+H) + |
| 65                    |                    | Free material | Powder<br>MS·APCI (m/z) : 320/322 (M+H) + |
| 66                    |                    | Free material | Powder<br>MS·APCI (m/z) : 330/332 (M+H) + |

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Reference example 67

Under argon atmosphere, to a solution of 4-chloro-3-fluorobenzaldehyde (10 g) in N,N-dimethylformamide (50 ml) was added 5 sodium cyanide (620 mg) at room temperature, and the mixture was stirred at the same temperature for 3 hours. Then, to the mixture was added dropwise a solution of ethyl acrylate (5.2 ml) in N,N-dimethylformamide (25 ml), and the resulting mixture was stirred at the room temperature for 3 hours. The reaction 10 mixture was poured into water and extracted with diethyl ether. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate=20:1) 15 to obtain ethyl 4-(4-chloro-3-fluorophenyl)-4-oxobutyrate (9.4 g) as pale yellowish powder.

MS·APCI (m/z): 259/261 (MH<sup>+</sup>)

Reference example 68

20

Under argon atmosphere, a mixture of succinic acid monoethyl ester monochloride (2.0 g), tributyl(3-thienyl)tin (5.44 g) and bis(triphenylphosphine) palladium chloride (853 mg) in dioxane (40 ml) was refluxed for 3 hours. After cooling, to the residue 25 was added a saturated aqueous sodiumhydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (solvent: hexane : ethyl acetate =6:1), and recrystallized from ethyl acetate-hexane to obtain ethyl 30 4-(3-thienyl)-4-oxobutyrate (1.4 g) as pale yellowish powder.

MS·APCI (m/z): 213 (MH<sup>+</sup>)

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Reference example 69

To a solution of ethyl 4-(5-chlorothiophen-2-yl)-4-oxobutyrate (900 mg) in dichloromethane (9 ml) was added bromine (200 µl) under ice-cooling, and after stirring at the same temperature for 30 minutes, the reaction mixture was warmed to room temperature and the mixture was stirred for one hour. The reaction mixture was poured into ice-water, and ethyl acetate and diethyl ether were added thereto. The organic layer was collected, washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain ethyl 3-bromo-4-(5-chlorothiophen-2-yl)-4-oxo-  
butyrate (1.22 g) as pale brownish liquid.

MS·APCI (*m/z*): 326/328 (MH<sup>+</sup>)

15

Reference examples 70 and 71

Corresponding starting compounds were treated in a manner similar to Reference example 69 to obtain the compounds shown in Table  
20 59 below.

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Table 59

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.               |
|-----------------------|--------------------|---------------|---------------------------------------|
| 70                    |                    | Free material | Oil<br>MS·APCI (m/z) : 337/339 (M+H)+ |
| 71                    |                    | Free material | Oil<br>MS·APCI (m/z) : 291/293 (M+H)+ |

## Reference example 72

5

to a mixture of (2-methylthio)pyrimidin-5-carboxylic acid sodium salt (1.50 g), ammonium chloride (2.09 g) and 1-hydroxybenzotriazole (1.27 g) in N,N-dimethylformamide (20 ml) were successively added 3-ethyl-1-(3-dimethylamino-10 propyl)carbodiimide hydrochloride (1.80 g) and triethylamine (6.5 ml) under ice-cooling, and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate, washed with water and brine, dried over 15 anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was digested with diethyl ether-ethyl acetate. Then, the suspension was cooled and the precipitate was filtered, and washed with diethyl ether-n-hexane to obtain (2-methylthio)pyrimidin-5-carb-20 oxamide (927 mg).

MS·APCI (m/z) : 170 (MH+)

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Reference example 73

Corresponding starting compounds were treated in a manner similar to Reference example 72 to obtain 4,5-dimethylthiophen-

5 2-carboxamide.

MS·APCI (m/z): 156 (MH<sup>+</sup>)

Reference example 74

10 To a suspension of 6-chloronicotinamide (1.50 g) in ethanol (30 ml) was added sodium hydride (1.88 g, 60% mineral oil), and the mixture was stirred at room temperature for 24 hours. Another portion of sodium hydride (940 mg, 60% mineral oil) was added to the mixture, and the resulting mixture was stirred at room  
15 temperature for 24 hours followed by refluxing for 4.5 hours. Then, the reaction mixture was cooled, a saturated aqueous ammonium chloride solution was added thereto and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent  
20 was removed under reduced pressure. The residue was triturated with diethyl ether to obtain 6-ethoxynicotinamide (1.05 g) as colorless powder.

MS·APCI (m/z): 167 (MH<sup>+</sup>)

25 Reference example 75

A mixture of (2-methylthio)pyrimidin-5-carboxamide (569 mg) and Lawesson's reagent (2.72 g) in chloroform (20 ml) was refluxed overnight. After cooling the reaction mixture, it was purified  
30 by NH silica gel column chromatography (solvent: ethyl acetate). The residue was triturated with diethyl ether and washed with n-hexane to obtain (2-methylthio)pyrimidin-5-carbothioamide (247 mg) as yellowish powder.

MS·APCI (m/z): 186 (MH<sup>+</sup>)

35

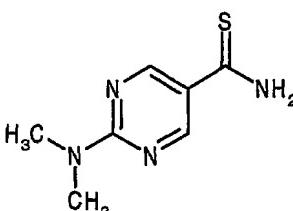
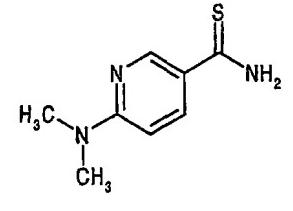
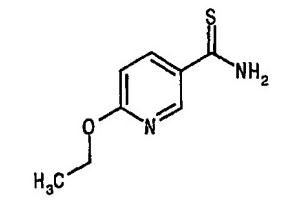
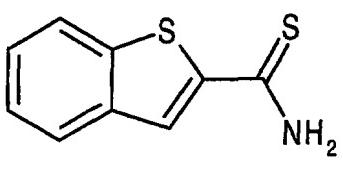
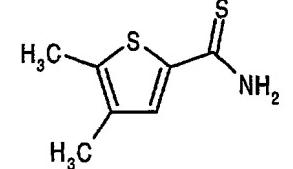
Reference examples 76 to 80

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Corresponding starting compounds were treated in a manner similar to Reference example 75 to obtain the compounds shown in Table 60 below.

5

Table 60

| Reference example No. | Chemical structure  | Salt          | Physical constant, etc.   |
|-----------------------|---|---------------|---|
| 76                    |    | Free material | Crystal<br>Melting point:<br>227.5-228.5 °C<br>MS·APCI (m/z) :<br>183 (M+H) + |
| 77                    |   | Free material | Powder<br>MS·APCI (m/z) :<br>182 (M+H) +                                      |
| 78                    |  | Free material | Powder<br>MS·APCI (m/z) :<br>183 (M+H) +                                      |
| 79                    |  | Free material | Powder<br>MS·APCI (m/z) :<br>194 (M+H) +                                      |
| 80                    |  | Free material | Powder<br>ESI·MS (m/z) :<br>170 (M-H)   |

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Reference example 81

- Corresponding starting compounds were treated in a manner similar to Reference example 13(1) to obtain methyl 5-(3-chloro-  
 5 4-fluorophenyl)oxazol-4-yl carboxylate.  
 MS·APCI (m/z) : 256/258 (MH<sup>+</sup>)

Reference examples 82 and 83

- 10 Corresponding starting compounds were treated in a manner similar to Reference example 13(2) to obtain the compounds shown in Table 61 below.

Table 61

15

| Reference example No. | Chemical structure | Salt | Physical constant, etc.                              |
|-----------------------|--------------------|------|--|
| 82                    |                    | HCl  | Powder<br>MS·APCI (m/z) : 136 (M+H) <sup>+</sup>     |
| 83                    |                    | HCl  | Powder<br>MS·APCI (m/z) : 188/190 (M+H) <sup>+</sup> |

Reference examples 84 to 87

Corresponding starting compounds were treated in a manner similar

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to Reference example 10(1) or Reference example 20(4) to obtain the compounds shown in Table 62 below.

Table 62

5

| Reference example No. | Chemical structure | Salt | Physical constant, etc.                   |
|-----------------------|--------------------|------|---|
| 84                    |                    | HCl  | Powder<br>MS·APCI (m/z) : 256/258 (M+H) + |
| 85                    |                    | HCl  | Powder<br>MS·APCI (m/z) : 228 (M+H) +     |
| 86                    |                    | HCl  | Powder<br>MS·APCI (m/z) : 223 (M+H)       |
| 87                    |                    | Free | Crystal<br>Melting point: 158-159°C       |

Reference examples 88 to 90

Corresponding starting compounds were treated in a manner similar  
10 to Reference example 20(3) to obtain the compounds shown in Table  
63 below.

Table 63

| Reference example No. | Chemical structure | Salt          | Physical constant, etc.                       |
|-----------------------|--------------------|---------------|---|
| 88                    |                    | Free material | Oily state<br>MS·APCI (m/z) : 284/286 (M+H) + |
| 89                    |                    | Free material | Oily state<br>MS·APCI (m/z) : 256 (M+H) +     |
| 90                    |                    | Free material | Oily state<br>MS·APCI (m/z) : 323 (M+H)       |

## Experimental example 1

5

Relaxation effect on potassium-induced contraction of isolated rabbit urinary bladder

Urinary bladder was isolated from Male NZW rabbits (2.0-3.5kg)  
 10 and immersed in ice-cold Krebs-bicarbonate solution (in mM: 118 NaCl, 4.7 KCl, 1.2, 2.5 CaCl<sub>2</sub>, MgSO<sub>4</sub>, 1.2 KH<sub>2</sub>PO<sub>4</sub>, 11 glucose, 25 NaHCO<sub>3</sub>). The urinary bladder was cut into longitudinal strips

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(5mm length, 3-4mm width) after mucosal layer was removed. Preparations were mounted in organ baths containing 10ml of Krebs solution maintained at 37°C and gassed with 95% O<sub>2</sub> /5% CO<sub>2</sub>. Accordingly, preparations were stretched with an initial tension 5 of 2.0±1.0g, and changes in isometric tension were measured by force-displacement transducer. The preparations were pre-contracted by changing organ-bath solution into high-K<sup>+</sup> (30mM) Krebs solution (in mM: 92.7 NaCl, 30 KCl, 1.2, 2.5 CaCl<sub>2</sub>, MgSO<sub>4</sub>, 1.2 KH<sub>2</sub>PO<sub>4</sub>, 11 glucose, 25 NaHCO<sub>3</sub>).

10

After stable tension was obtained, compounds were added into organ baths cumulatively (10<sup>-6</sup>M-10<sup>-4</sup>M). The effects of compounds were expressed as a percentage of the maximum relaxation produced by 0.1mM papaverine. 50% relaxation concentration (EC<sub>50</sub>) was 15 calculated and EC<sub>50</sub> value range ( $\mu$ M) of the compounds of the present invention was shown in the following Table 64 with a rank of A, B or C. These ranges are as mentioned below.

3≥C>1≥B>0.5≥A

20

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Table 64

| Preparation example No. | EC <sub>50</sub> value range | Preparation example No. | EC <sub>50</sub> value range |
|-------------------------|------------------------------|-------------------------|------------------------------|
| 5                       | C                            | 9 5                     | C                            |
| 1 0                     | C                            | 9 6                     | C                            |
| 1 3                     | A                            | 9 7                     | B                            |
| 1 4                     | C                            | 9 9                     | B                            |
| 1 6                     | C                            | 1 0 4                   | B                            |
| 1 9                     | A                            | 1 0 8                   | C                            |
| 2 5                     | A                            | 1 2 0                   | A                            |
| 3 0                     | C                            | 1 2 1                   | C                            |
| 3 3                     | A                            | 1 3 1                   | C                            |
| 3 4                     | C                            | 1 3 2                   | B                            |
| 3 5                     | C                            | 1 3 6                   | B                            |
| 3 6                     | C                            | 1 4 0                   | C                            |
| 3 8                     | C                            | 1 5 2                   | C                            |
| 3 9                     | C                            | 1 5 5                   | C                            |
| 4 9                     | B                            | 1 5 8                   | C                            |
| 5 0                     | C                            | 1 6 8                   | B                            |
| 5 1                     | A                            | 1 6 9                   | C                            |
| 5 2                     | A                            | 1 7 0                   | C                            |
| 5 3                     | B                            | 1 7 1                   | C                            |
| 5 4                     | C                            | 1 7 2                   | C                            |
| 5 5                     | C                            | 1 7 3                   | C                            |
| 5 6                     | B                            | 1 8 0                   | C                            |
| 5 7                     | C                            | 1 8 1                   | B                            |
| 5 9                     | C                            | 1 8 2                   | A                            |
| 6 0                     | C                            | 1 8 7                   | B                            |
| 6 1                     | C                            | 1 9 7                   | C                            |
| 8 1                     | C                            | 2 3 5                   | B                            |
| 8 4                     | A                            | 2 4 0                   | B                            |
| 8 6                     | B                            | 2 4 3                   | A                            |
| 8 7                     | C                            | 2 4 4                   | C                            |
| 8 8                     | C                            | 2 4 5                   | C                            |
| 9 0                     | C                            | 2 4 6                   | B                            |

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Table 64 (Contd.)

| Preparation example No. | EC <sub>50</sub> value range | Preparation example No. | EC <sub>50</sub> value range |
|-------------------------|------------------------------|-------------------------|------------------------------|
| 247                     | C                            | 362                     | C                            |
| 248                     | C                            | 363                     | C                            |
| 249                     | C                            | 364                     | C                            |
| 252                     | B                            | 365                     | C                            |
| 253                     | B                            | 366                     | A                            |
| 255                     | C                            | 367                     | B                            |
| 256                     | A                            | 372                     | C                            |
| 257                     | A                            | 373                     | C                            |
| 262                     | C                            | 374                     | C                            |
| 265                     | C                            | 377                     | C                            |
| 267                     | A                            | 378                     | C                            |
| 268                     | A                            | 431                     | B                            |
| 269                     | A                            | 432                     | A                            |
| 271                     | B                            | 434                     | B                            |
| 272                     | A                            | 435                     | B                            |
| 273                     | C                            | 437                     | A                            |
| 275                     | A                            | 438                     | C                            |
| 277                     | B                            | 441                     | C                            |
| 278                     | B                            | 444                     | C                            |
| 279                     | A                            | 445                     | C                            |
| 280                     | A                            | 446                     | A                            |
| 281                     | A                            | 451                     | C                            |
| 282                     | B                            | 452                     | A                            |
| 283                     | A                            | 453                     | B                            |
| 284                     | C                            | 454                     | C                            |
| 285                     | C                            | 455                     | C                            |
| 286                     | A                            | 458                     | A                            |
| 287                     | A                            | 459                     | C                            |
| 288                     | A                            | 462                     | B                            |
| 339                     | C                            | 464                     | C                            |
| 350                     | C                            | 469                     | C                            |
| 355                     | A                            | 473                     | B                            |

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Table 64 (Contd.)

| Preparation example No. | EC <sub>50</sub> value range | Preparation example No. | EC <sub>50</sub> value range |
|-------------------------|------------------------------|-------------------------|------------------------------|
| 4 7 8                   | A                            | 5 7 8                   | B                            |
| 4 7 9                   | A                            | 5 7 9                   | B                            |
| 4 8 6                   | C                            | 5 8 4                   | C                            |
| 4 8 7                   | B                            | 5 8 6                   | A                            |
| 5 0 3                   | C                            | 5 8 7                   | B                            |
| 5 0 4                   | C                            | 5 9 0                   | A                            |
| 5 0 6                   | B                            | 5 9 4                   | A                            |
| 5 0 7                   | A                            | 5 9 6                   | C                            |
| 5 1 1                   | A                            | 5 9 7                   | A                            |
| 5 1 2                   | B                            | 6 0 0                   | A                            |
| 5 1 4                   | B                            | 6 0 1                   | B                            |
| 5 1 7                   | A                            | 6 0 9                   | B                            |
| 5 2 4                   | C                            | 6 1 0                   | A                            |
| 5 3 1                   | C                            | 6 1 2                   | A                            |
| 5 7 2                   | C                            | 6 1 6                   | C                            |
| 5 7 4                   | C                            | 6 2 3                   | C                            |
| 5 7 5                   | A                            | 6 2 6                   | C                            |
| 5 7 6                   | B                            | 6 3 9                   | C                            |

## Experimental example 2

5

Inhibitory effect on the rhythmic bladder contractions induced by substance P in anesthetized rats

- For the experiments, Sprague-Dawley female rats (9 to 12 weeks old) weighing between 200 to 300 g were used. After urethane anesthetization (subcutaneously administered with a dose of 1.2 g/kg), cannulae were placed in both right and left femoral veins. One intravenous catheter was used for administration of compounds, and the other was for the substance P (0.33 µg/kg/min) infusion.
- We also cannulated into ureter to pass urine. Polyethylene catheters were inserted into carotid artery for continuous monitoring of arterial blood pressure and heart rate. For continuous infusion, transurethral bladder catheter was

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inserted into the bladder through the urethra and tied in place by a ligature around the urethral orifice. One end of the catheter was attached to a pressure transducer in order to measure intravesical pressure. The other end of the catheter was used  
5 for infusion of saline into the bladder. After stabilization of blood pressure and heart rate and after the bladder was emptied, cystometry was performed by filling the bladder slowly with about 0.6 ml of saline. After about 10 minutes, intravenous infusion of substance P (0.33 $\mu$ g/kg/min) was started for stabilization  
10 of the micturition reflex. Compounds were administered after stable rhythmic bladder contraction was obtained over 15 minutes. All compounds were dissolved or suspended in saline containing 0.5% Tween 80 for intravenous administration (0.1 ml/kg). The rhythmic contraction frequency and the intravesical pressure  
15 were observed for 35 minutes after administration of the test compound.

As a result, the compounds of the present invention decreased the frequency of bladder rhythmic contraction without changing  
20 the amplitude of contraction. Also, we determined a time (minute) during which the frequency of the rhythmic contraction had been completely inhibited by administering 0.25 mg/kg of the compound. A 100% inhibition time (minute) of the selected compounds of the present invention is shown in the following  
25 Table 65 with a rank of A, B or C. These ranges are as mentioned below.

A $\geq$ 20 $>$ B $\geq$ 10 $>$ C (minute)

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Table 65

| Preparation example No. | 100% inhibition time range | Preparation example No. | 100% inhibition time range |
|-------------------------|----------------------------|-------------------------|----------------------------|
| 1 3                     | C                          | 9 0                     | B                          |
| 1 4                     | A                          | 9 3                     | B                          |
| 1 6                     | B                          | 9 9                     | B                          |
| 2 4                     | C                          | 1 0 2                   | C                          |
| 2 5                     | B                          | 1 0 4                   | A                          |
| 2 7                     | B                          | 1 0 7                   | B                          |
| 2 8                     | B                          | 1 0 8                   | B                          |
| 3 0                     | B                          | 1 2 0                   | C                          |
| 3 1                     | A                          | 1 2 2                   | B                          |
| 3 4                     | A                          | 1 2 3                   | C                          |
| 4 3                     | C                          | 1 2 4                   | B                          |
| 4 6                     | B                          | 1 2 5                   | C                          |
| 4 7                     | B                          | 1 3 2                   | B                          |
| 4 8                     | C                          | 1 3 3                   | C                          |
| 5 0                     | C                          | 1 3 6                   | C                          |
| 5 3                     | C                          | 1 3 7                   | C                          |
| 5 4                     | B                          | 1 4 2                   | C                          |
| 5 5                     | B                          | 1 4 3                   | C                          |
| 5 6                     | B                          | 1 4 4                   | C                          |
| 5 9                     | B                          | 1 5 2                   | B                          |
| 6 1                     | A                          | 1 5 3                   | B                          |
| 6 2                     | C                          | 1 5 5                   | B                          |
| 6 3                     | C                          | 1 5 6                   | B                          |
| 6 7                     | B                          | 1 5 8                   | C                          |
| 7 2                     | C                          | 1 6 0                   | C                          |
| 8 0                     | B                          | 1 6 2                   | C                          |
| 8 3                     | B                          | 1 6 4                   | B                          |
| 8 5                     | C                          | 1 6 6                   | B                          |
| 8 6                     | B                          | 1 6 8                   | B                          |
| 8 7                     | B                          | 1 7 1                   | B                          |
| 8 8                     | B                          | 1 7 2                   | C                          |

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Table 65 (contd.)

| Preparation example No. | 100% inhibition time range | Preparation example No. | 100% inhibition time range |
|-------------------------|----------------------------|-------------------------|----------------------------|
| 176                     | C                          | 256                     | C                          |
| 181                     | B                          | 257                     | B                          |
| 182                     | B                          | 258                     | C                          |
| 187                     | B                          | 259                     | B                          |
| 189                     | C                          | 260                     | A                          |
| 197                     | C                          | 262                     | C                          |
| 198                     | C                          | 263                     | C                          |
| 201                     | C                          | 267                     | C                          |
| 233                     | C                          | 268                     | C                          |
| 234                     | C                          | 269                     | B                          |
| 235                     | B                          | 270                     | B                          |
| 236                     | C                          | 271                     | C                          |
| 237                     | C                          | 272                     | B                          |
| 238                     | C                          | 273                     | C                          |
| 239                     | C                          | 274                     | B                          |
| 240                     | C                          | 275                     | A                          |
| 241                     | C                          | 276                     | C                          |
| 242                     | C                          | 277                     | C                          |
| 243                     | A                          | 278                     | B                          |
| 244                     | B                          | 279                     | C                          |
| 245                     | C                          | 280                     | C                          |
| 246                     | B                          | 281                     | C                          |
| 247                     | C                          | 282                     | B                          |
| 248                     | B                          | 283                     | C                          |
| 249                     | B                          | 284                     | B                          |
| 250                     | B                          | 285                     | B                          |
| 251                     | C                          | 286                     | C                          |
| 252                     | C                          | 287                     | B                          |
| 253                     | A                          | 288                     | C                          |
| 254                     | C                          | 289                     | B                          |
| 255                     | B                          | 290                     | B                          |

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Table 65 (contd.)

| Preparation example No. | 100% inhibition time range | Preparation example No. | 100% inhibition time range |
|-------------------------|----------------------------|-------------------------|----------------------------|
| 2 9 1                   | C                          | 4 3 3                   | C                          |
| 2 9 2                   | C                          | 4 3 4                   | B                          |
| 2 9 3                   | C                          | 4 3 5                   | B                          |
| 2 9 5                   | B                          | 4 3 6                   | C                          |
| 2 9 6                   | C                          | 4 3 7                   | B                          |
| 3 3 1                   | A                          | 4 3 8                   | C                          |
| 3 3 7                   | C                          | 4 3 9                   | C                          |
| 3 3 8                   | C                          | 4 4 0                   | C                          |
| 3 4 8                   | C                          | 4 4 1                   | B                          |
| 3 5 0                   | B                          | 4 4 2                   | C                          |
| 3 5 1                   | C                          | 4 4 3                   | C                          |
| 3 6 2                   | A                          | 4 4 4                   | B                          |
| 3 6 3                   | C                          | 4 4 5                   | A                          |
| 3 6 4                   | B                          | 4 4 6                   | C                          |
| 3 6 5                   | B                          | 4 4 7                   | B                          |
| 3 6 6                   | C                          | 4 4 8                   | C                          |
| 3 6 7                   | A                          | 4 4 9                   | B                          |
| 3 6 8                   | B                          | 4 5 0                   | B                          |
| 3 6 9                   | B                          | 4 5 1                   | B                          |
| 3 7 0                   | C                          | 4 5 2                   | B                          |
| 3 7 1                   | C                          | 4 5 3                   | C                          |
| 3 7 3                   | C                          | 4 5 4                   | A                          |
| 3 7 4                   | C                          | 4 5 5                   | B                          |
| 3 7 5                   | C                          | 4 5 6                   | C                          |
| 3 7 6                   | C                          | 4 5 7                   | B                          |
| 3 7 7                   | C                          | 4 5 8                   | B                          |
| 3 7 8                   | C                          | 4 5 9                   | C                          |
| 3 8 0                   | C                          | 4 6 2                   | C                          |
| 4 3 0                   | B                          | 4 6 4                   | C                          |
| 4 3 1                   | B                          | 4 6 6                   | B                          |
| 4 3 2                   | C                          | 4 6 7                   | A                          |

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Table 65 (contd.)

| Preparation example No. | 100% inhibition time range | Preparation example No. | 100% inhibition time range |
|-------------------------|----------------------------|-------------------------|----------------------------|
| 4 6 9                   | B                          | 5 6 9                   | A                          |
| 4 7 0                   | B                          | 5 7 0                   | A                          |
| 4 7 2                   | A                          | 5 7 1                   | A                          |
| 4 7 3                   | A                          | 5 7 2                   | C                          |
| 4 7 4                   | C                          | 5 7 3                   | B                          |
| 4 7 5                   | B                          | 5 7 4                   | B                          |
| 4 7 6                   | B                          | 5 7 5                   | B                          |
| 4 7 8                   | B                          | 5 7 6                   | A                          |
| 4 7 9                   | C                          | 5 7 7                   | B                          |
| 4 8 2                   | C                          | 5 7 8                   | B                          |
| 4 8 4                   | B                          | 5 7 9                   | C                          |
| 4 8 6                   | B                          | 5 8 0                   | C                          |
| 4 8 7                   | C                          | 5 8 2                   | A                          |
| 5 0 3                   | A                          | 5 8 3                   | B                          |
| 5 0 4                   | C                          | 5 8 4                   | A                          |
| 5 0 5                   | B                          | 5 8 5                   | C                          |
| 5 1 1                   | C                          | 5 8 6                   | B                          |
| 5 1 2                   | B                          | 5 8 7                   | A                          |
| 5 1 3                   | C                          | 5 8 8                   | C                          |
| 5 1 4                   | B                          | 5 8 9                   | A                          |
| 5 1 6                   | B                          | 5 9 0                   | B                          |
| 5 1 7                   | C                          | 5 9 1                   | B                          |
| 5 2 2                   | B                          | 5 9 4                   | C                          |
| 5 2 3                   | B                          | 5 9 6                   | B                          |
| 5 2 4                   | B                          | 6 0 0                   | A                          |
| 5 2 5                   | A                          | 6 0 1                   | A                          |
| 5 2 9                   | B                          | 6 0 8                   | B                          |
| 5 3 0                   | C                          | 6 0 9                   | B                          |
| 5 3 1                   | C                          | 6 1 0                   | B                          |
| 5 3 2                   | C                          | 6 1 1                   | B                          |
| 5 6 8                   | A                          | 6 1 2                   | A                          |

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Table 65 (contd.)

| Preparation example No. | 100% inhibition time range | Preparation example No. | 100% inhibition time range |
|-------------------------|----------------------------|-------------------------|----------------------------|
| 6 1 3                   | C                          | 6 2 4                   | C                          |
| 6 1 4                   | C                          | 6 2 6                   | C                          |
| 6 1 5                   | B                          | 6 2 7                   | C                          |
| 6 1 6                   | B                          | 6 2 8                   | C                          |
| 6 1 7                   | B                          | 6 3 0                   | C                          |
| 6 2 2                   | B                          | 6 3 9                   | C                          |
| 6 2 3                   | C                          |                         |                            |

Experimental example 3

5

Large conductance calcium-activated K channel opening action in isolated rabbit bladder

The urinary bladder strips were prepared according to the same manner as described in Experimental example 1. Briefly, the isolated urinary bladder was cut into longitudinal strips in ice-cold Krebs-bicarbonate solution, and mounted in organ baths. The initial tension was 2.0+/-1.0g. The preparations were contracted by high-K<sup>+</sup>(20mM or 60mM) Krebs solution.

15

Active ingredients of the present invention showed relaxation effect on 20mM K<sup>+</sup>-contracted preparation and the effect was blocked by iberiotoxin, a selective large conductance calcium-activated K channel blocker.

20

Also in *in vivo* animal study, pre-administration of iberiotoxin (0.15 mg/kg, intravenous administration) reduced inhibitory effect of active ingredients in the present invention on the rhythmic bladder contraction.

25 It is suggested from the results that the active ingredients

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of the present invention have a detrusor relaxing activity through the large conductance calcium-activated K channel.

Thus, it was shown that the compounds which are active ingredients

5 of the present invention were effective for prophylaxis and treatment of diseases such as pollakiuria, urinary incontinence and the like through the large conductance calcium-activated K channel opening activity.

10 The nitrogen-containing 5-membered heterocyclic compound (I) or a pharmaceutically acceptable salt which is an active ingredient of the present invention has an excellent large conductance calcium-activated K channel opening activity and hyperpolarizes a membrane electric potential of cells, so that  
15 it is useful for a prophylactic, relief and/or treatment agent of, for example, hypertension, asthma, premature birth, irritable bowel syndrome, chronic heart failure, angina, cardiac infarction, cerebral infarction, subarachnoid hemorrhage, cerebral vasospasm, cerebral hypoxia, peripheral blood vessel  
20 disorder, anxiety, male-pattern baldness, erectile dysfunction, diabetes, diabetic peripheral nerve disorder, other diabetic complication, sterility, urolithiasis and pain accompanied thereby, pollakiuria, urinary incontinence, nocturnal enuresis, and the like.

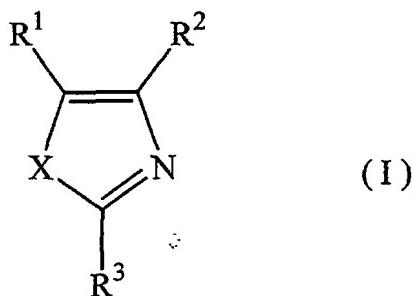
25

Also, the nitrogen-containing 5-membered heterocyclic compound (I) or a pharmaceutically acceptable salt has a low toxicity, so that it has high safety as a medicine.

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Claims:

1. A large conductance calcium-activated K channel opener comprising as an active ingredient a nitrogen-containing  
 5 5-membered heterocyclic compound represented by the following formula (I):



10 wherein X represents N-R<sup>4</sup>, O or S, R<sup>1</sup> and R<sup>2</sup> are different from each other and each independently represents hydrogen atom, a halogen atom, carboxyl group, a substituted or unsubstituted amino group, a substituted or unsubstituted lower alkyl group, a lower alkoxy carbonyl group, a substituted or unsubstituted lower alkenyl group, a cyclo-lower alkyl group, a substituted or unsubstituted carbamoyl group, a substituted or unsubstituted aryl group,  
 15 a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted heterocyclic group-substituted carbonyl group, R<sup>3</sup> represents a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted lower alkyl group, and R<sup>4</sup> represents hydrogen atom or a substituted or unsubstituted lower alkyl group,  
 20 or a pharmaceutically acceptable salt thereof.

2. The large conductance calcium-activated K channel opener according to Claim 1, wherein R<sup>1</sup> and R<sup>2</sup> each independently represent (1) hydrogen atom, (2) a halogen atom, (3) a carboxyl group, (4) an amino group which may be substituted by at least  
 30

one selected from formyl group, a lower alkyl group, a lower alkanoyl group, a lower alkylsulfonyl group and a lower alkoxycarbonyl group, (5) a lower alkyl group which may be substituted by at least one selected from a halogen atom,

5 hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, aminosulfonyl group, a halogenosulfonyl group, amidinothio group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group,

10 trifluoromethyl group, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a lower alkoxycarbamoyl group, a lower alkylsulfonylcarbamoyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxycarbonyl group,

15 a heterocyclic group, a heterocyclic group-substituted carbamoyl group, a heterocyclic group-substituted lower alkylcarbamoyl group and a heterocyclic group-substituted sulfonylcarbamoyl group, (6) a lower alkoxycarbonyl group, (7) a lower alkenyl group which may be substituted by carboxyl group

20 or a lower alkoxycarbonyl group, (8) a cyclo-lower alkyl group, (9) a carbamoyl group which may be substituted by at least one selected from a lower alkyl group, a lower alkoxy group and a lower alkylsulfonyl group, (10) an aryl group which may be substituted by at least one selected from nitro group, amino

25 group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, trifluoromethyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino

30 group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkylsulfonylamino group and a phenyl-lower alkoxy group, (11) a heterocyclic group which may be substituted by at least one selected from nitro

35 group, hydroxyl group, formyl group, carbamoyl group, cyano group, amino group, carboxyl group, a lower alkoxycarbonyl

group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group, or (12) a heterocyclic group-substituted carbonyl group which may be substituted by at least one selected from nitro group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, a lower alkoxy carbonyl group, a halogen atom,

5 a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkanoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower

10 alkylsulfamoyl group; R<sup>3</sup> is (1) an aryl group which may be substituted by at least one selected from cyano group, nitro group, amino group, a halogen atom, trifluoromethyl group, carboxyl group, hydroxyl group, carbamoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkylamino-lower

15 alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group, a lower alkanoyl group, a lower alkanoyloxy group, a lower alkanoyloxy-lower alkyl group, sulfo group, a lower alkylthio group, a lower alkylthio-lower alkyl

20 group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group and a lower alkylsulfinyl group, (2) a heterocyclic group which may be substituted by at least one selected from oxo group, cyano group, nitro group, amino group, a halogen atom, carboxyl group, hydroxyl group, formyl group, carbamoyl group, a mono-

25 or di-lower alkylamino group, a N-lower alkyl-N-cyclo-lower alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkyl group, a lower alkoxy carbonyl group,

30 a lower alkanoyl group, sulfo group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group, a

35

- lower alkylsulfinyl group and a heterocyclic group, or (3) a alkyl group which may be substituted by at least one selected from hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, a mono- or di-lower alkylamino group, a
- 5 lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a halogen atom, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, sulfamoyl group, a mono- or di-lower
- 10 alkylsulfamoyl group, a lower alkoxycarbonyl group and a heterocyclic group; and R<sup>4</sup> is (1) hydrogen atom, or (2) a lower alkyl group which may be substituted by a mono- or di-lower alkylamino group.
- 15 3. The large conductance calcium-activated K channel opener according to Claim 1 or 2, wherein R<sup>1</sup> is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) an aryl group which may be substituted by one or two halogen atoms, or (3)
- 20 a heterocyclic group which may be substituted by a halogen atom, R<sup>2</sup> is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) a heterocyclic group which may be substituted by a halogen atom, or (3) an aryl group which may be substituted by one or
- 25 two halogen atoms; R<sup>3</sup> is (1) a heterocyclic group which may be substituted by one or two groups selected from amino group, a halogen atom, a lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group and a lower alkylthio group, or (2) an aryl group which may be substituted by amino group, a
- 30 halogen atom, a lower alkyl group, a lower alkylthio group, a lower alkoxy group or a mono- or di-lower alkylamino group; and R<sup>4</sup> is hydrogen atom or a lower alkyl group.
4. The large conductance calcium-activated K channel opener
- 35 according to Claim 3, wherein R<sup>1</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a lower

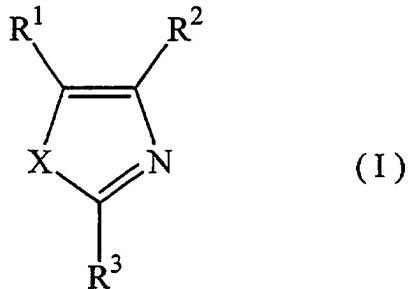
- alkyl group substituted by a tetrazolyl group, (4) a phenyl group which may be substituted by one or two halogen atoms, or (5) a thienyl group which may be substituted by a halogen atom; R<sup>2</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxy-5 carbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a thienyl group which may be substituted by a halogen atom, or (5) a phenyl group which may be substituted by one or two halogen atoms; and R<sup>3</sup> is (1) a benzothienyl group which may be substituted by a halogen atom,  
10 (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkyl group, a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be  
15 substituted by a di-lower alkylamino group or a lower alkylthio group, (5) a thienyl group which may be substituted by one or two lower alkyl groups, (6) thieno[3,2-b]pyridyl group, (7) benzofuryl group, (8) dihydrobenzofuryl group or (9) an indolyl group which may be substituted by a lower alkyl group.  
20
5. The large conductance calcium-activated K channel opener according to Claim 4, wherein X is O or S; R<sup>1</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a phenyl group which may be substituted by one  
25 or two halogen atoms, or (4) a thienyl group which may be substituted by a halogen atom; R<sup>2</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a thienyl group which may be substituted by a halogen atom, or  
30 (4) a phenyl group which may be substituted by one or two halogen atoms; and R<sup>3</sup> is (1) a benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkoxy group or a di-lower  
35 alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group, (5) a thienyl group

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which may be substituted by a di-lower alkyl group, (6) thieno[3,2-b]pyridyl group, or (7) an indolyl group which may be substituted by a lower alkyl group.

- 5 6. Use of the large conductance calcium-activated K channel opener as set forth in any one of Claims 1 to 5 for manufacture of a medicament for use in the treatment or prophylaxis of pollakiuria or urinary incontinence.
- 10 7. A method for prophylaxis and/or treatment of pollakiuria or urinary incontinence which comprises administering an effective amount of the large conductance calcium-activated K channel opener as set forth in any one of Claims 1 to 5 to a patient of pollakiuria or urinary incontinence or a patient who
- 15 has a possibility of causing pollakiuria or urinary incontinence.

8. Use of a compound of formula (I)



- 20 wherein X represents N-R<sup>4</sup>, O or S, R<sup>1</sup> and R<sup>2</sup> are different from each other and each independently represents hydrogen atom, a halogen atom, carboxyl group, a substituted or unsubstituted amino group, a substituted or unsubstituted lower alkyl group, a lower alkoxy carbonyl group, a substituted or unsubstituted lower alkenyl group, a cyclo-lower alkyl group, a substituted or unsubstituted carbamoyl group, a substituted or unsubstituted aryl group,
- 25 a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted heterocyclic group-substi-
- 30

- tuted carbonyl group, R<sup>3</sup> represents a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted lower alkyl group, and R<sup>4</sup> represents hydrogen atom or a  
5 substituted or unsubstituted lower alkyl group,  
or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in the treatment or prophylaxis of pollakiuria or urinary incontinence.
- 10 9. The use according to Claim 8, wherein R<sup>1</sup> and R<sup>2</sup> each independently represent (1) hydrogen atom, (2) a halogen atom, (3) a carboxyl group, (4) an amino group which may be substituted by at least one selected from formyl group, a lower alkyl group, a lower alkanoyl group, a lower alkylsulfonyl group and a lower  
15 alkoxy carbonyl group, (5) a lower alkyl group which may be substituted by at least one selected from a halogen atom, hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, aminosulfonyl group, a halogenosulfonyl group, amidinothio group, a mono- or di-lower alkylamino group, a lower  
20 alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a lower alkoxy carbamoyl group,  
25 a lower alkylsulfonylcarbamoyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxy carbonyl group, a heterocyclic group, a heterocyclic group-substituted carbamoyl group, a heterocyclic group-substituted lower alkylcarbamoyl group and a heterocyclic group-substituted  
30 sulfonylcarbamoyl group, (6) a lower alkoxy carbonyl group, (7) a lower alkenyl group which may be substituted by carboxyl group or a lower alkoxy carbonyl group, (8) a cyclo-lower alkyl group, (9) a carbamoyl group which may be substituted by at least one selected from a lower alkyl group, a lower alkoxy group and a lower alkylsulfonyl group, (10) an aryl group which may be substituted by at least one selected from nitro group, amino  
35

group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, trifluoromethyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkylsulfonylamino group and a phenyl-lower alkoxy group, (11) a heterocyclic group which may be substituted by at least one selected from nitro group, hydroxyl group, formyl group, carbamoyl group, cyano group, amino group, carboxyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group, or (12) a heterocyclic group-substituted carbonyl group which may be substituted by at least one selected from nitro group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkanoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group; R<sup>3</sup> is (1) an aryl group which may be substituted by at least one selected from cyano group, nitro group, amino group, a halogen atom, trifluoromethyl group, carboxyl group, hydroxyl group, carbamoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group, a lower alkanoyl group, a lower alkanoyloxy group, a lower alkanoyloxy-lower alkyl group, sulfo group, a lower alkylthio group, a lower alkylthio-lower alkyl

group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group and a lower alkylsulfinyl group, (2) a heterocyclic group which may be substituted by at least one selected from oxo group, cyano group, nitro group, amino group, a halogen atom, carboxyl group, hydroxyl group, formyl group, carbamoyl group, a mono- or di-lower alkylamino group, a N-lower alkyl-N-cyclo-lower alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkyl group, a lower alkoxycarbonyl group, a lower alkanoyl group, sulfo group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group, a lower alkylsulfinyl group and a heterocyclic group, or (3) a alkyl group which may be substituted by at least one selected from hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a halogen atom, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxycarbonyl group and a heterocyclic group; and R<sup>4</sup> is (1) hydrogen atom, or (2) a lower alkyl group which may be substituted by a mono- or di-lower alkylamino group.

10. The use according to Claim 8 or 9, wherein R<sup>1</sup> is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) an aryl group which may be substituted by one or two halogen atoms, or (3) a heterocyclic group which may be substituted by a halogen atom, R<sup>2</sup> is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) a heterocyclic group which may be substituted by a halogen atom, or (3) an aryl group which may be substituted by one or two halogen atoms; R<sup>3</sup> is (1) a heterocyclic group which may be

substituted by one or two groups selected from amino group, a halogen atom, a lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group and a lower alkylthio group, or (2) an aryl group which may be substituted by amino group, a 5 halogen atom, a lower alkyl group, a lower alkylthio group, a lower alkoxy group or a mono- or di-lower alkylamino group; and R<sup>4</sup> is hydrogen atom or a lower alkyl group.

11. The use according to Claim 10, wherein R<sup>1</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a phenyl group which may be substituted by one or two halogen atoms, or (5) a thienyl group which may be substituted by a halogen atom; R<sup>2</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a thienyl group which may be substituted by a halogen atom, or (5) a phenyl group which may be substituted by one or two halogen atoms; and R<sup>3</sup> is (1) a benzothienyl group which may be substituted by a 15 halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkyl group, a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group or a lower alkylthio group, (5) a thienyl group which may be substituted by one or two lower alkyl groups, (6) thiopheno[3,2-b]pyridyl group, (7) benzofuryl group, (8) dihydrobenzofuryl group or (9) a 20 indolyl group which may be substituted by a lower alkyl group.

30 12. The use according to Claim 11, wherein X is O or S; R<sup>1</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a phenyl group which may be substituted by one or two halogen atoms, or (4) a thienyl group which may be substituted by a halogen atom; R<sup>2</sup> is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3)

a thienyl group which may be substituted by a halogen atom, or  
(4) a phenyl group which may be substituted by one or two halogen atoms; and R<sup>3</sup> is (1) a benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be 5 substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group, (5) a thienyl group 10 which may be substituted by a di-lower alkyl group, (6) thiopheno[3,2-b]pyridyl group, or (7) an indolyl group which may be substituted by a lower alkyl group.

13. A compound represented by the formula (I) wherein X is O, 15 one of R<sup>1</sup> and R<sup>2</sup> is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group, a lower alkoxy carbonyl-lower alkyl group or a lower alkyl group substituted by a tetrazolyl group, and R<sup>3</sup> is a substituted or unsubstituted 20 aryl group or a substituted or unsubstituted heterocyclic group, or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 13, wherein R<sup>3</sup> is (1) an aryl group which may be substituted by one or two substituents 25 selected from a halogen atom, a di-lower alkylamino group, a lower alkylthio group and a lower alkoxy group, or (2) a heterocyclic group which may be substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group and a mono- or 30 di-lower alkylamino group.

15. The compound according to Claim 14, wherein one of R<sup>1</sup> and R<sup>2</sup> is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group or a lower alkoxy- 35 carbonyl-lower alkyl group; the aryl group is phenyl group; and the heterocyclic group is a thienyl group, a pyridyl group, a

pyrimidinyl group, a benzothienyl group, a benzofuryl group, a dihydrobenzofuryl group, an indolyl group or a thieno[3,2-b]pyridyl group.

5    16. The compound according to Claim 14, wherein R<sup>3</sup> is a phenyl group which is substituted by a halogen atom or a lower alkylthio group; a thienyl group which is substituted by one or two lower alkyl groups; a pyrimidinyl group which is substituted by di-lower alkylamino group; a benzothienyl group which may be  
10    substituted by a halogen atom; an indolyl group which may be substituted by a lower alkyl group; or a thieno[3,2-b]pyridyl group.

15    17. A compound represented by the formula (I) wherein X is S, one of R<sup>1</sup> and R<sup>2</sup> is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group, a lower alkoxy carbonyl-lower alkyl group or a lower alkyl group substituted by a tetrazolyl group, and R<sup>3</sup> is a substituted or unsubstituted heterocyclic group, where said heterocyclic  
20    group is selected from a pyridyl group, a pyrimidinyl group, a benzothienyl group, an indolyl group and a thieno[3,2-b]-pyridyl group, or a pharmaceutically acceptable salt thereof.

25    18. The compound according to Claim 17, wherein R<sup>3</sup> is a heterocyclic group which may be substituted by one or two substituents selected from a halogen atom, a lower alkoxy group, a mono- or di-lower alkyl group, a lower alkylthio group and a mono- or di-lower alkylamino group, where said heterocyclic group is selected from a pyridyl group, a pyrimidinyl group,  
30    a benzothienyl group, and a thieno[3,2-b]pyridyl group.

35    19. The compound according to Claim 18, wherein one of R<sup>1</sup> and R<sup>2</sup> is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group or a lower alkoxy-carbonyl-lower alkyl group; R<sup>3</sup> is a pyridyl group which may be substituted by a di-lower alkylamino group; a pyrimidinyl group

which may be substituted by a mono- or di-lower alkylamino group; or a benzothienyl group which may be substituted by a halogen atom.

- 5    20. 4-(5-Chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)-thiazol-5-yl acetic acid,  
      5-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)-oxazol-4-yl acetic acid,  
      4-(5-chlorothiophen-2-yl)-2-(4-methoxyphenyl)thiazol-5-yl  
10    acetic acid,  
      5-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-oxazol-4-yl acetic acid,  
      4-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)thiazol-5-yl acetic acid,  
15    4-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyridin-5-yl)thiazol-5-yl acetic acid,  
      5-(4-chlorophenyl)-2-(4-fluorophenyl)oxazol-4-yl acetic acid,  
      5-(4-chlorophenyl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic  
20    acid,  
      4-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)oxazol-5-yl acetic acid,  
      5-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)oxazol-4-yl acetic acid,  
25    4-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)-thiazol-5-yl acetic acid,  
      5-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic acid,  
      4-(4-chlorophenyl)-2-(4-methoxyphenyl)thiazol-5-yl acetic  
30    acid,  
      5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-4-yl acetic acid,  
      5-(5-chlorothiophen-2-yl)-2-(6-fluorobenzo[b]thiophene-2-yl)oxazol-4-yl acetic acid,  
35    5-(3-thienyl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic acid,  
      5-(5-chlorothiophen-2-yl)-2-(2-thieno[3,2-b]pyridyl)-

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- oxazol-4-yl acetic acid,  
5-(3-fluoro-4-chlorophenyl)-2-(2-benzo[b]thienyl)oxazol-4-  
yl acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)thiazol-4-yl  
5 acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(4-methylthiophenyl)oxazol-4-yl  
acetic acid,  
4-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-5-yl  
acetic acid,  
10 5-(5-chlorothiophen-2-yl)-2-(4-chlorophenyl)oxazol-4-yl  
acetic acid,  
4-(3-fluoro-4-chlorophenyl)-2-(4-methoxyphenyl)thiazol-5-yl  
acetic acid,  
4-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-  
15 thiazol-5-yl acetic acid,  
4-(3-fluoro-4-chlorophenyl)-2-(4-fluorophenyl)thiazol-5-yl  
acetic acid,  
4-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyridin-5-yl)-  
thiazol-5-yl acetic acid,  
20 4-(5-chlorothiophen-2-yl)-2-(4-N,N-dimethylaminophenyl)-  
thiazol-5-yl acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(N-methylindol-2-yl)oxazol-4-yl  
acetic acid,  
5-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-  
25 thiazol-4-yl acetic acid;  
or a lower alkyl ester thereof;  
or a pharmaceutically acceptable salt thereof.
21. A pharmaceutical composition comprising a therapeutically  
30 effective amount of a compound as set forth in any one of Claims  
13 to 20 in admixture with a therapeutically acceptable carrier  
or diluent.
22. Use of the compound as set forth in any one of Claims 13  
35 to 20 for manufacture of a medicament for use in the prophylaxis  
and/or treatment for pollakiuria or urinary incontinence.

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23. The use according to Claim 22, wherein the compound is as set forth in Claim 20.
24. Use of a compound as set forth in any one of Claims 13 to 5 20 for manufacture of a large conductance calcium-activated K channel opener.
25. The use according to Claim 24, wherein the compound is as set forth in Claim 20.  
10
26. A large conductance calcium-activated K channel opener comprising as an active ingredient the compound as set forth in any one of Claims 13 to 20.
- 15 27. The large conductance calcium activated K channel opener according to Claim 26, wherein the compound is as set forth in Claim 20.
- 20 28. A method for prophylaxis and/or treatment of pollakiuria or urinary incontinence which comprises administering an effective amount of the compound as set forth in any one of Claims 13 to 20 to a patient of pollakiuria or urinary incontinence or a patient who has a possibility of causing pollakiuria or urinary incontinence.  
25
29. The method according to Claim 28, wherein the compound is as set forth in Claim 20.

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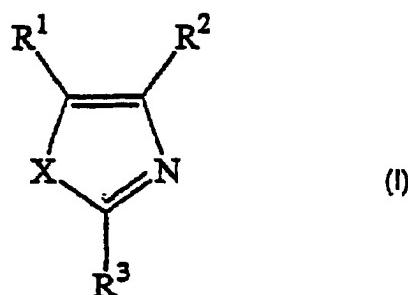
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(54) Title: IMIDAZOLE, THIAZOLE AND OXAZOLE DERIVATIVES AND THEIR USE FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT AND/OR PREVENTION OF POLLAKIURIA OR URINARY INCONTINENCE



(57) Abstract: A large conductance calcium-activated K channel opener comprising as an active ingredient a nitrogen-containing 5-membered heterocyclic compound represented by the following formula (I): wherein X represents N-R<sup>4</sup>, O or S, R<sup>1</sup> and R<sup>2</sup> each independently represent hydrogen, halogen, carboxyl, amino, lower alkyl, lower alkoxy carbonyl, lower alkenyl, cyclo-lower alkyl, carbamoyl, aryl, heterocyclic or heterocyclic-substituted carbonyl group, R<sup>3</sup> represents aryl, heterocyclic or lower alkyl group, and R<sup>4</sup> represents hydrogen or lower alkyl group, or a pharmaceutically acceptable salt thereof and its use for the preparation of a medicament for the prophylaxis and/or treatment of pollakiuria or urinary incontinence.

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# INTERNATIONAL SEARCH REPORT

PCT/JP 02/03723

| A. CLASSIFICATION OF SUBJECT MATTER |            |            |             |             |            |
|-------------------------------------|------------|------------|-------------|-------------|------------|
| IPC 7                               | C07D233/54 | C07D233/64 | C07D233/68  | C07D263/30  | C07D263/32 |
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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, BIOSIS, PAJ, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages                                    | Relevant to claim No. |
|----------|---|-----------------------|
| X        | DE 31 28 492 A (NATTERMANN A & CIE)<br>3 February 1983 (1983-02-03)<br>page 6, line 16 -page 7, line 4; claims<br>1-3 | 1-5                   |
| X        | DE 31 28 453 A (NATTERMANN A & CIE)<br>3 February 1983 (1983-02-03)<br>claims 1-12                                    | 1-5                   |
| X        | US 4 356 185 A (CAVALLA JOHN F)<br>26 October 1982 (1982-10-26)<br>claims 1-4   | 1-5                   |
| X        | GB 1 574 583 A (WYETH JOHN & BROTHER LTD)<br>10 September 1980 (1980-09-10)<br>page 4; claim 1; table 1               | 1-5                   |
|          | -/-   |                       |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### Special categories of cited documents :

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# INTERNATIONAL SEARCH REPORT

PCT/JP 02/03723

|  |  |  |  |
|--|--|--|--|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b>   |  |  |  |
| IPC 7 A61K31/422 A61K31/426 A61K31/427 A61K31/443 A61K31/4436<br>A61K31/506 A61P13/00  |  |  |  |
| According to International Patent Classification (IPC) or to both national classification and IPC  |  |  |  |
| <b>B. FIELDS SEARCHED</b>  |  |  |  |
| Minimum documentation searched (classification system followed by classification symbols)  |  |  |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  |  |  |  |
| Electronic data base consulted during the International search (name of data base and, where practical, search terms used)   |  |  |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>  |  |  |  |
| Category   | Citation of document, with indication, where appropriate, of the relevant passages                     | Relevant to claim No.  |  |
| X  | US 4 127 663 A (CAVALLA JOHN F)<br>28 November 1978 (1978-11-28)<br>claim 1                            | 1-5  |  |
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| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.   |  | <input checked="" type="checkbox"/> Patent family members are listed in annex. |  |
| * Special categories of cited documents :  |  |  |  |
| "A" document defining the general state of the art which is not considered to be of particular relevance   |  |  |  |
| "E" earlier document but published on or after the International filing date   |  |  |  |
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| "P" document published prior to the International filing date but later than the priority date claimed   |  |  |  |
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| "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |  |  |  |
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| Date of the actual completion of the International search  |  | Date of mailing of the International search report                             |  |
| 26 August 2002   |  |  |  |
| Name and mailing address of the ISA  |  | Authorized officer   |  |
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016  |  | Tardi, C   |  |

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
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### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims 1-5 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims 1-5 is impossible. Consequently, the search has been restricted to the compounds given in Formula I which appear to represent the preferred embodiments, i.e. where X = O, S or N, one of R1 and R2 is acetic acid, the other one being an optionally substituted thienyl or phenyl, and R3 being an optionally substituted alkyl, aryl or heterocyclic group.

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